DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2006

WEDNESDAY, APRIL 6, 2005

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:30 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter, Cochran, and Harkin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF ELIAS ZERHOUNI, M.D., DIRECTOR

ACCOMPANIED BY:

DR. JAMES F. BATTEY, JR., M.D., Ph.D., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

DR. ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DR. ANDREW VON ESCHENBACH, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning, ladies and gentlemen. The hour of 9:30 has—having arrived, we will proceed with the hearing of the Appropriations Subcommittee on Labor, Health and Human Services, Education. Today our hearing will focus on the work of the National Institutes of Health, which I have characterized as the crown jewel of the Federal Government, and perhaps the only jewel of the Federal Government.

We have the distinguished director, Elias Zerhouni, Dr. Elias Zerhouni, with us today, and other members. We have in the past had all of the directors of the Institutes, and it is not realistic to hear from that number of witnesses, and knowing of the important work, we have decided this year to limit the witnesses to those who have presidential appointments. We have also included Dr. Battey because of some recent issues as to the new policy on ethics, which will be a subject of some of our discussion here today.

Before proceeding further, just a word or two about my health. I have a lot of questions about my health. I had my fourth treat-

ment last Friday and I am on the job. During the 2-week recess when I could not travel abroad, I was in Washington most of the time, and aside from an involuntary new hair style, I'm accommodating to all of the rigors of the situation. I find that among all of the alternatives, the best alternative is to come to work and fight tigers, and we've got a lot of tigers around here, and fighting tigers is a great distraction and a great cure. So just that little bit of recommendation to the foremost scientists in the world, just how to handle one person's temporary medical problem.

The work of the National Institutes of Health is a vital matter for America and for the world. Senator Harkin, who will be along in a few moments, and I, as is well known, have taken the lead on the increase in funding where we have moved from some $12 billion to $28 billion. This year the funding was almost flat, really not accommodating even inflation. Senator Harkin and I offered an amendment to add $1.5 billion to the budget resolution, which passed.

It's been a long struggle. The first time we tried to add money to the budget resolution we lost 63 to 37, and we went back with a sharp pencil and established the priorities. That's become a virtual impossibility now with the very heavy demands on our subcommittee on education and health and community development block grants and many other items, and worker safety. It will be a battle to keep that extra $1.5 billion in terms of real dollars that we will have.

We will want to discuss the issues of the new standards of ethics. When the issue came up before the House of Representatives, there was I think a, diplomatically stated, a pretty stern tone taken. When the matter came before this subcommittee, we reviewed the matter with Dr. Zerhouni and said we'd look forward to his response.

But we also gave the people who were being charged an opportunity to come in and speak for themselves and to defend themselves on an extemporaneous basis. They were in the audience. They were welcome to come up and to do—and to talk. We had that hearing back on January 22, 2004.

It's always a difficult matter to prescribe a cure, medically or politically or ethically. It may well be that there are some revisions which are necessary, and we're going to make some suggestions and engage in some dialogue. But the ultimate decisions have to rest with the professionals who are in the field.

One word about stem cells, which we will take up in the course of the hearing. There is great concern about the Federal policy on stem cells contrasted with what is happening in the States with the $3 billion budget in California and the lure of top scientists to California. Now Massachusetts is coming in with a program. We have discussed in this subcommittee the concerns about a brain drain going to Europe. This is something that we have to deal with.

There was very strong sentiment in the Congress about broadening the use of stem cells, moving away not necessarily from nuclear transplantation. We're not talking about creating another Dolly or about those sort of tactics, but just to use the stem cells which otherwise will be thrown away. There are hundreds of thou-

sands which were created for in vitro fertilization and they're not being used, and they could be used to cure diseases.

We understand the situation with the administration, Dr. Zerhouni, and the White House point of view, and I have suggested to you before that you might look for some greater latitude for advocacy within the administration. You're very respectful and you're very diplomatic and your voice might be heard and be influential.

I've had an opportunity to talk to the President about the matter. He was in Pennsylvania 44 times during the campaign, and I was with him on most of the occasions. We had a lot of time to talk on the plane and in the car. His views are pretty firm, but so are mine, and so are, I think, a majority of the Congress, as you see with what's happening in the House. Senator Harkin, Senator Feinstein, Senator Hatch, Senator Kennedy, and I have re-introduced legislation. So that's a big matter for the research future of America and the world.

That's longer than I usually talk, but since there are no other members present, I felt a little more latitude. Dr. Zerhouni, we welcome you here. We thank you for taking on this tough job and we look forward to your testimony.

SUMMARY STATEMENT OF DR. ELIAS A. ZERHOUNI

Dr. ZERHOUNI. Thank you, Mr. Chairman, and first and foremost, let me tell you about our admiration for your continuing service while you're fighting cancer, and we're looking forward to seeing you support NIH, support medical research as you have in the past for many years to come.

I would like to also——

Senator SPECTER. Is there any shortcut to—Dr. Zerhouni—to returning Arlen Specter the kind of head of hair that Elias Zerhouni has?

Dr. ZERHOUNI. I would be very happy to share.

Senator SPECTER. I hope the camera will focus on Dr. Zerhouni's hair, so we don't just get this verbally.

Dr. ZERHOUNI. I will do everything to share that with you, sir.

Senator SPECTER. I don't want share, I want my own, Dr. Zerhouni.

Dr. ZERHOUNI. I have submitted for the record written testimony.

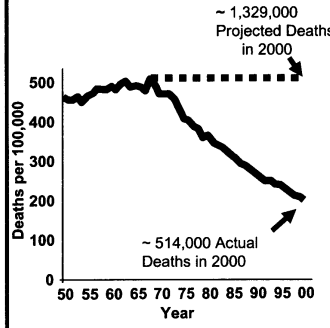
Senator SPECTER. Your full statement will be made a part of the record, Dr. Zerhouni, and in accordance with our standard practice, to the extent you can summarize, that would be helpful to leave the maximum amount of time for questions and answers. We have a vote scheduled at 10:00 and we have the new Prime Minister of the Ukraine speaking. But this is a very important hearing and I will return after the vote so we do full justice to the issues which we have here today.

THE PAST, THE PRESENT, AND THE FUTURE FOR NIH

Dr. ZERHOUNI. Thank you. I will do so. First and foremost, let me summarize for us with a few slides where NIH is and where the budget is heading. Clearly, NIH has, as you said, been the crown jewel of medical research and of the Federal Government in promoting and advancing, through research, better health.

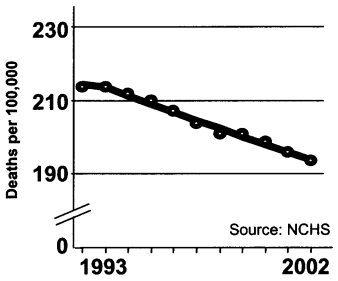
Continuous Progress in Health Care

Heart Disease



Reduction of coronary heart disease age-adjusted death rates: 815,000 deaths prevented in 2000

Cancer

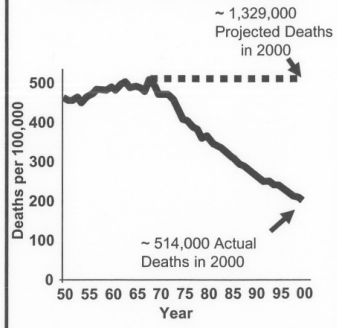


Men: Mortality reduced in 11/15 common cancers

Women: Mortality reduced in 8/15 common cancers

Continuous Progress in Health Care

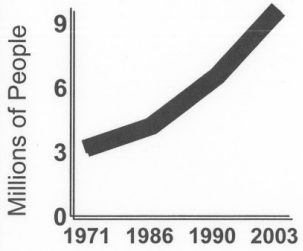
Heart Disease



Reduction of coronary heart disease age-adjusted death rates: 815,000 deaths prevented in 2000

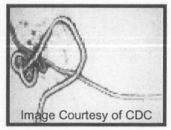
Cancer

Trajectory of Survivorship

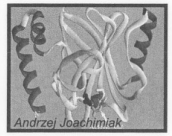


	Survival Rate (%) 1974-76	1992-99
All Cancers	50	63
Breast	75	87
Colon	50	62
Hodgkin's Disease	71	84
Prostate	67	98

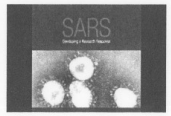
Infectious Agents



Ebola: First vaccine in trial in 2003

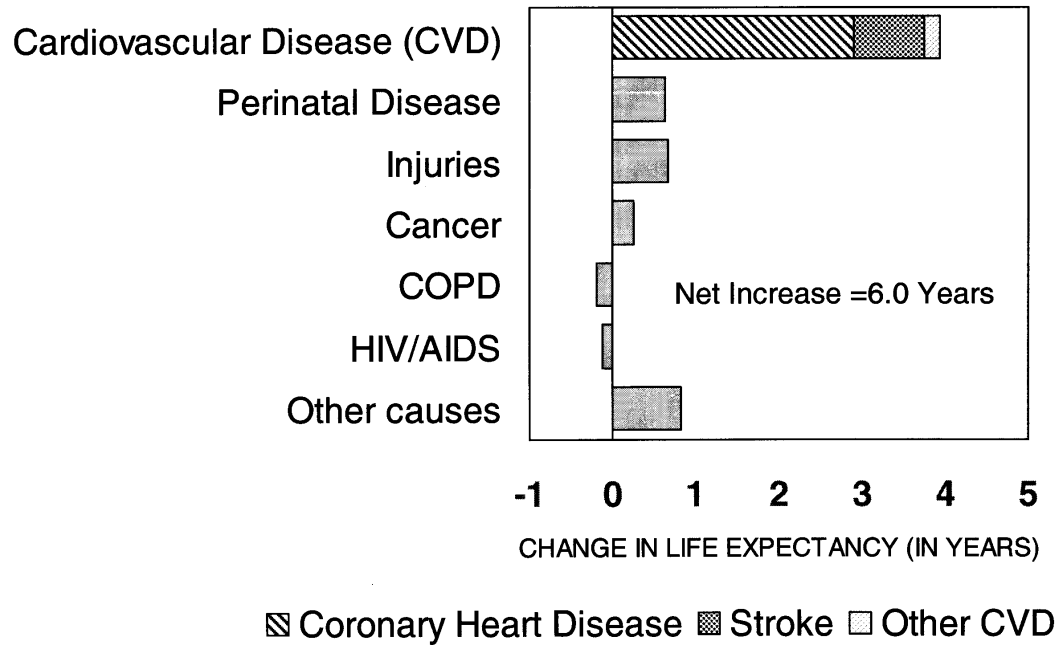


Anthrax: Crystallized Anthrax, new drug targets



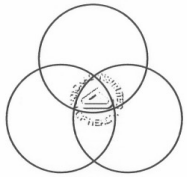
SARS: Identified in < 1 month. First vaccine in trial in 2004

Contributions to Change in Life Expectancy
U.S., 1970 to 2000



Strengthening the NIH Vision

FY 2004



NIH Roadmap for Medical Research

- Involves entire NIH
- Accelerates basic research discoveries
- Speeds translation of those discoveries into clinical practice
- Explicitly addresses roadblocks slowing pace of medical progress

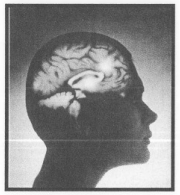
FY 2005

NIH Strategic Plan for Obesity Research

- Involves 19 Institutes and Centers
- Research focuses on preventing and treating obesity:
  - lifestyle modification
  - pharmacologic
  - surgical
  - other medical approaches

Image © *Time magazine*, June 2004

FY 2006



NIH Neuroscience Blueprint

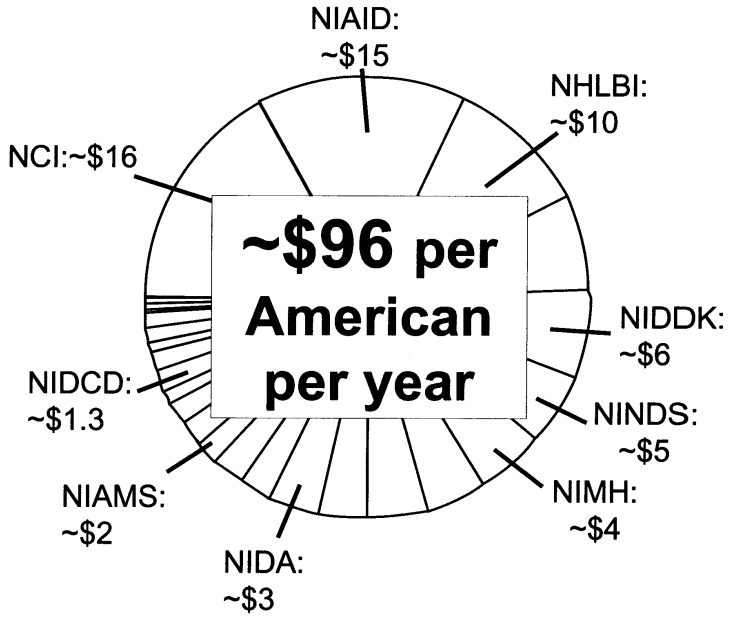
- Involves 15 Institutes and Centers
- Develops Tools
- Creates resources
- Public and private partnerships
- Speeds treatment discovery

The Scope of the Challenge

NIH invests ~$96/American/year into research to stem the rising burden of :

Hundreds of Common Diseases

>6000 Rare Diseases



NIH Budget: Five High Priorities

Supporting Both New and Established Scientists

- **New and Competing Research Project Grants** **+ 247 Grants**

Accelerating Research for Treatments and Prevention Strategies

- **NIH Roadmap for Medical Research** **+ $98 M**

Developing Countermeasures for Biological and Chemical Threats

- **Biodefense Research** **+ $56 M**

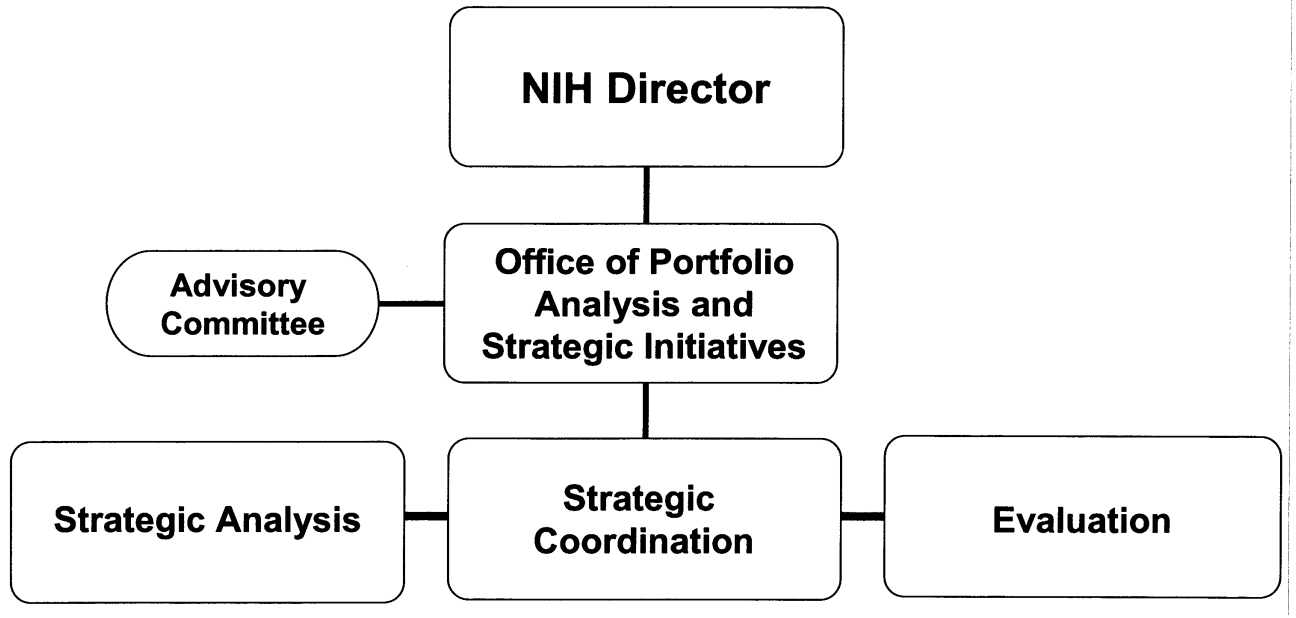
Addressing Rising Burden of Nervous System Diseases

- **NIH Neuroscience Blueprint** **+ $26 M**

Seizing Scientific Opportunity

- **HIV-AIDS Vaccine Development** **+ $100 M**

21st Century Tools for Managing 21st Century Science




NIH
Ideas
People
Resources
Leadership

I'll show you some results that I think all of us know. In heart disease, we've had a 60 percent reduction in mortality over the past 30 years, primarily due to discoveries in terms of metabolism, of cholesterol, in terms of inflammation, in terms of the management of hypertension. You can see over the slides there that we've seen for the first time a marked decrease in both mortality and morbidity, with 815,000 lives saved this year—in 2000.

For the first time, over the past 10 years we're seeing a very real decrease in cancer mortality. The National Cancer Institute should really be commended for these results. We've seen, for example, mortality reduced in 11 of the 15 most common cancers in men and in 8 of the 15 most common cancers in women. We're continuing to see increased survivorship for cancer with a markedly increased number of Americans living with cancer today, from 3 to 9 million and rising.

I think you can see the survival rates between 1974, 1976, 1992, and 1999, and you can see improvements in all cancers. But you can see also in very specific cancers, survival rates right now in breast cancer are 87 percent, colon cancer 62 percent, Hodgkin's disease 84 percent, and prostate cancer 98 percent.

We're continuing to do research on infectious agents and the new threats of biodefense agents. And you can see that in 2003 for the first time we've developed an effective vaccine against ebola virus. Anthrax, we've crystallized the anthrax toxin and have identified new drug targets.

In SARS, I'd like to remind you that because of the doubling of the budget that you have spearheaded and the research and the new tools that were made available to human genome research, we were able to identify the SARS virus in less than a month. Today there is the first vaccine in trial already in the works, and two more have been developed as well.

So I think that the investment that you have really helped us with has paid off and is paying off. We're continuing to strengthen the NIH vision by doing systematic coordination across all the Institutes. In 2004 we presented the NIH Roadmap for Medical Research that involves all the Institutes and really engages in areas where no single Institute can do the job. In 2005, we announced the trans-NIH plan for obesity research, and in 2006, this year, the NIH neuroscience blueprint.

The scope of the challenge is enormous, as you well know. We have hundreds of common diseases and 6,000 rare diseases to take care of. Clearly, the budget that we have is large, $28 billion. But from our standpoint of scientists and physicians, we look at it on a per-American basis. When you look at that, what you realize is that we have to manage $96 per American per year. The NCI manages $16 per American per year to combat all cancer, NIAID $15, NHLBI $10. It is in this context that we have to invest our dollars to make the most impact on our health care costs, which are fast rising and come to $5,500 per American per year.

Clearly, the budget this year is going to have to lead to difficult choices, and we've established priorities, such as the support of new and established scientists with new grants. We've increased the number of grants available for competition, obviously at the expense of inflation factors and other choices we had to make. We are

accelerating research for treatments and prevention strategies through the NIH Roadmap for Medical Research. We're continuing to develop countermeasures for biological and chemical threats. This year we're announcing the neuroscience blueprint. We think that even though we have difficult budgets, it's important to do the right thing even if it's not the right budgetary time.

Again, this year we have many new candidate vaccines——

Senator SPECTER. What do you mean, Dr. Zerhouni, by doing the right thing even though if it's not the right budgetary time?

MAKING THE RIGHT CHOICES

Dr. ZERHOUNI. What I mean is despite the fact that there is a flat budget there are scientific opportunities in neurosciences, behavioral sciences. And we believe, with the 15 Institute directors that are primarily responsible for this area of science, that it was important to have a coordinated plan to advance our knowledge of the brain and the nervous system and the impact of behavioral—and behavioral factors on health.

This year we have several new vaccines available for HIV/AIDS that will need to be tested, and that is very costly. We have moved $100 million within our tight budget to the priorities that we believe in 2006 will allow us to test for the first time very promising vaccines for HIV/AIDS.

Senator SPECTER. Where do you take that money from?

Dr. ZERHOUNI. Basically we've moved it from all categories of the total AIDS budget over the past 2 years, as we predicted with Dr. Fauci, that in 2006 we will need to engage in larger-scale clinical trials of HIV vaccines.

Last, I think that it is clear that as the organization known as NIH has grown more complex, it is also important to coordinate and understand better the portfolio of investments we're making, especially when you consider that we are managing $96 per American per year. You want to make sure that all of that investment is maximally utilized. We are announcing the creation of a new Office of Portfolio Analysis and Strategic Initiatives in 2006 and requesting budgetary support for that office to do both strategic analysis of what is it we've done——

PROPOSAL TO CREATE THE OFFICE OF PORTFOLIO ANALYSIS AND STRATEGIC INITIATIVES

Senator SPECTER. What do you mean or need by budgetary support?

Dr. ZERHOUNI. We've requested a budget line for the Office of the Director to create this office and support it.

Senator SPECTER. How much is that line?

Dr. ZERHOUNI. We've started with a $2 million request.

Senator SPECTER. $2 million?

PREPARED STATEMENTS

Dr. ZERHOUNI. Yes. This office is going to allow us to develop better coding, better understanding of our databases, and coordinate them across Institutes so that we can have a standard way of looking at the entire activities of the Agency. We will work through the

Institutes and centers to coordinate, as we've shown in the past with the trans-NIH obesity plan, that we could in fact find areas of synergy and improve on them, and obviously evaluate whether or not we are. As you often ask us: "What have we accomplished?" I think we need to evaluate it systematically to show you and the American people supporting us the results of this research.

[The statements follows:]

PREPARED STATEMENT OF DR. ELIAS ZERHOUNI

Mr. Chairman, Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the Office of the Director (OD). The fiscal year 2006 budget includes, $385,195,000, an increase of $27,149,000 over the fiscal year 2005 enacted level of $358,046,000 comparable for transfers proposed in the President's request. The OD provides leadership, coordination, and guidance in the formulation of policy and procedures related to biomedical research and research training programs. The OD also is responsible for a number of special programs and for management of centralized support services to the operations of the entire NIH.

The OD guides and supports research by setting priorities; allocating funding among these priorities; developing policies based on scientific opportunities and ethical and legal considerations; maintaining peer review processes; providing oversight of grant and contract award functions and of intramural research; communicating health information to the public; facilitating the transfer of technology to the private sector; and providing fundamental management and administrative services such as budget and financial accounting, and personnel, property, and procurement management, administration of equal employment practices, and plant management services, including environmental and public safety regulations of facilities. The principal OD offices providing these activities include the Office of Extramural Research (OER), the Office of Intramural Research (OIR), and the Offices of: Science Policy; Communications and Public Liaison; Legislative Policy and Analysis; Equal Opportunity; Budget; and Management. This request contains funds to support the functions of these offices.

In addition, the OD also maintains several trans-NIH offices and programs to foster and encourage research on specific, important health needs. I will now discuss the budget request for the OD in greater detail.

NIH ROADMAP FOR MEDICAL RESEARCH

The NIH Roadmap for Medical Research supports trans-agency research and training programs aimed at accelerating the pace of discovery and improving the translation of research findings into health interventions. The development of new tools and technologies will help scientists understand intricate cellular processes and will make large volumes of biologic data publicly available for analysis and use in other model systems. Nanomedicine concept development awards are defining the scope of future centers to explore molecular inventions and interventions for curing disease or repairing tissues. Innovative team approaches will facilitate the creation of new biomedical and behavioral interdisciplinary fields and contribute to our understanding of complex diseases and conditions. Studies examining outcomes such as pain, fatigue and obesity will be enhanced by NIH Roadmap projects supporting the integration of behavioral and social sciences with biomedical and physical sciences. The clinical research initiatives are exploring ways to promote the integration and extension of clinical research networks, support translational research, and facilitate the coordination and harmonization of clinical research policies across federal agencies. Critical to these new efforts will be an infusion of trained scientists and clinical researchers at all stages of their careers, able to apply interdisciplinary and multidisciplinary approaches to complex biomedical problems. And for the first time, physicians, nurses and dentists are being trained together to become leaders in this clinical research community. These and other projects will enhance the capacity of scientists to harness the knowledge base for specific applications in all areas of investigation. The fiscal year 2006 budget request for NIH Roadmap for Medical Research is $83,000,000, an increase of $23,280,000 over the fiscal year 2005 level.

THE OFFICE OF AIDS RESEARCH

The Office of AIDS Research (OAR) plays a unique role at NIH, establishing a roadmap for the AIDS research program. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Our response

to the AIDS epidemic requires a unique and complex multi-institute, multi-disciplinary, global research program. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of the NIH Institutes and Centers. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently, allowing NIH to pursue a united research front against the global AIDS epidemic. OAR oversees the development of the annual comprehensive NIH AIDS-related research plan and budget, based on scientific consensus about the most compelling scientific priorities and opportunities that will lead to better therapies and prevention strategies for HIV disease. The Plan serves as the framework for developing the annual AIDS research budget for each Institute and Center; for determining the use of AIDS-designated dollars; and for tracking and monitoring those expenditures. OAR also identifies and facilitates multi-institute participation in priority areas of research and facilitates NIH involvement in international AIDS research activities. The fiscal year 2006 budget request for OAR is $60,899,000, which is the same as the fiscal year 2005 level.

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health (ORWH), the focal point for women's health research for the Office of the Director, strengthens, enhances and supports research related to diseases, disorders, and conditions that affect women, and sex/gender studies on differences/similarities between men and women; ensures that women are appropriately represented in biomedical and biobehavioral research studies supported by the NIH to facilitate analyses by sex/gender; and develops opportunities for the advancement of women in biomedical careers and investigators in women's health research. These ORWH efforts are in full partnership with the NIH Institutes and Centers. New research has been expanded in the ORWH-funded Specialized Centers of Research through interdisciplinary research in women's health and sex and gender factors and through the unique ORWH interdisciplinary career development program that fosters the mentored development of junior faculty and assists them in bridging advanced training towards a goal of research independence. The fiscal year 2006 budget request is $41,363,000, an increase of $148,000 over the fiscal year 2005 level.

THE OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

The NIH has a long history of funding health-related behavioral and social sciences research, and the results of this work have contributed significantly to our understanding, treatment, and prevention of disease. The Office of Behavioral and Social Sciences Research (OBSSR) furthers NIH's ability to capitalize on the scientific opportunities that exist in behavioral and social sciences research by providing leadership in identifying and implementing research programs that are likely to improve our understanding of the processes underlying health and disease and provide directions for intervention. OBSSR works to integrate a behavioral and social science approach across the programs of the NIH.

In response to a 2004 Institute of Medicine study entitled, "Improving Medical Education: Enhancing the Behavioral and Social Science Content of Medical School Curricula", OBSSR developed a program to promote the design and implementation of medical school curricula with coverage of behavioral and social sciences. This program will provide a mechanism whereby medical school students will receive training about issues such as the influence of psychological, biological, and social factors on health and disease; the role of physicians' beliefs, behaviors, and values in patient care; managing difficult physician-patient interactions; and the impact of policy on health behaviors and patient care. In addition to the benefits realized by individual physicians in training, funded medical schools may develop the infrastructures to permanently integrate behavioral and social sciences into their curricula. To continue such groundbreaking work in the behavioral and social sciences, the fiscal year 2006 budget request for OBSSR is $26,185,000, an increase of $94,000 over the fiscal year 2005 level.

THE OFFICE OF DISEASE PREVENTION

The primary mission of the Office of Disease Prevention (ODP) is to stimulate disease prevention research across the NIH and to coordinate and collaborate on related activities with other federal agencies as well as the private sector. There are several other offices within the ODP organizational structure.

The Office of Medical Applications of Research (OMAR) has as its mission to work with NIH Institutes, Centers, and Offices to assess, translate and disseminate the results of biomedical research that can be used in the delivery of important health interventions to the public. The ODP has two additional specific programs/offices that place emphasis on particular aspects of the prevention and treatment of disease the Office of Dietary Supplements (ODS) and the Office of Rare Diseases (ORD).

In fiscal year 2006, the ODS within ODP requests a budget of $27,078,000, an increase of $97,000 over the fiscal year 2005 level. ODS promotes the scientific study of the use of dietary supplements by supporting investigator-initiated research, and stimulating research through the conduct of conferences and presentations at national and international meetings. Other current ODS efforts include:

—Sponsorship of systematic review of the relationship between omega-3 fatty acids and a number of clinical indications, particularly coronary heart disease.
—Collaborations for the development, validation, and dissemination of analytical methods and reference materials for dietary supplements.
—Support and development of databases of dietary supplement information including:
  —National Health and Nutrition Examination Survey (NHANES);
  —Collaboration with USDA to develop an analytically-based database of dietary supplement ingredients;
  —Plan to contract for development of a dietary supplement label database;
  —International Bibliographic Information on Dietary Supplements (IBIDS);
  —CARDS, a database of federally funded research on dietary supplements.
—Collaboration with other federal agencies to develop a coordinated approach to assessment of the health effects of bioactive factors in food and dietary supplements. Publishes Fact Sheets on dietary supplements for consumers.

Another component of ODP, the ORD, was formally established through the Rare Diseases Act of 2002, Public Law 107–280. The budget request for fiscal year 2006 for ORD is $15,649,000, an increase of $56,000 over the fiscal year 2005 level. The following are four highlights of ORD activities: (1) An Extramural Rare Diseases Clinical Research Network that involves 10 consortia, more than 70 sites, and 30 patient support organizations for almost 50 rare diseases. Thirty-three clinical protocols are under development. (2) The Rare Diseases Intramural Research Program is a collaborative effort between the ORD and the National Human Genome Research Institute at the NIH Clinical Center. Recently, the program initiated annual contracts for 25 molecular diagnostic tests for specific rare diseases that will be made available by the contractor to the public at reasonable cost. (3) ORD also cofunds annually approximately 100 scientific conferences for scientific opportunities or where research is lagging or lacking. (4) The newly established Trans-NIH Rare Diseases Research Working Group is developing an assessment of rare diseases biospecimen collection, storage, and delivery issues, of genetic tests in extramural research programs, and plans for a conference on amyloidosis.

THE OFFICE OF SCIENCE EDUCATION

The Office of Science Education (OSE) develops science education programs to enhance efforts to attract young people to biomedical and behavioral science careers and to improve science literacy in both adults and children. The OSE creates programs to improve science education in schools (the *NIH Curriculum Supplement Series*); creates programs that stimulate interest in health and medical science careers (*LifeWorks Web site*); creates programs to advance public understanding of medical science, research, and careers; and advises NIH leadership about science education issues. Programs target diverse populations including under-served communities, women, and minorities, with a special emphasis on the teachers of students from Kindergarten through grade 12. The OSE Web site is a central source of information about available education resources and programs. http://science.education.nih.gov. The fiscal year 2006 budget request for OSE is $3,878,000, the same as the fiscal year 2005 level.

LOAN REPAYMENT AND SCHOLARSHIP PROGRAM

The NIH, through the Office of Loan Repayment and Scholarship (OLRS), administers the Loan Repayment and Undergraduate Scholarship Programs. The NIH Loan Repayment Programs (LRPs) seek to recruit and retain highly qualified physicians, dentists, and other health professionals with doctoral-level degrees to biomedical and behavioral research careers by countering the growing economic disincentives to embark on such careers, using as an incentive the repayment of educational loans. There are loan repayment programs designed to attract individuals to clinical research, pediatric research, health disparities research, and contracep-

tion and infertility research, and to attract individuals from disadvantaged backgrounds into clinical research. The AIDS, intramural Clinical, and General Research Loan Repayment Programs are designed to attract investigators and physicians to the NIH's intramural research and research training programs. The NIH Undergraduate Scholarship Program (UGSP) is a scholarship program designed to support and enhance the training of undergraduate students from disadvantaged backgrounds in biomedical research careers and employment at the NIH.

The fiscal year 2006 budget request for OLRS is $7,213,000, the same as the fiscal year 2005 level.

OFFICE OF PORTFOLIO ANALYSIS AND STRATEGIC INITIATIVES

In fiscal year 2006, the NIH plans to create a new office within the Office of the Director—the Office of Portfolio Analysis and Strategic Initiatives (OPASI)—which will provide tools to facilitate planning for trans-NIH initiatives, including an improved process for collecting IC data on expenditures on various diseases, conditions, and research fields, and improvements in data about burden of disease. The office will also develop, with input from the ICs, common processes and formats, where necessary, for the conduct of NIH-wide planning and evaluation. For trans-NIH planning efforts, the office will seek broad public input—from the public, health care providers, policymakers, and scientists—in addition to soliciting advice from within NIH. The office will also coordinate and make more effective use of the NIH-wide evaluation process. The budget request for OPASI is $2,000,000.

Thank you, Mr. Chairman for giving me the opportunity to present this statement; I will be pleased to answer questions that the Committee may have.

NATIONAL INSTITUTES OF HEALTH BUILDINGS AND FACILITIES PROGRAM

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the Buildings and Facilities (B&F) Program for fiscal year 2006, a sum of $81,900,000.

ROLE IN THE RESEARCH MISSION

State-of-the-science research and support facilities are a vital part of the research enterprise. The National Institutes of Health's (NIH) Buildings and Facilities (B&F) program designs, constructs, repairs and improves the agency's portfolio of laboratory, clinical, animal, administrative and support facilities at its six installations in four states. These facilities house researchers from the NIH Institutes' and Centers'(ICs) intramural basic, translational, and clinical research programs; science administrators who oversee NIH's grants; the NIH leadership, and various programs that support agency operations. The fiscal year 2006 B&F budget request focuses on the need for responsible utilization and stewardship of NIH's past and recent investments in the "bricks and mortar" of the research enterprise. In order to stay abreast of the changing needs of the NIH programs, it is imperative that we provide reliable, safe and secure research support facilities that are appropriately equipped, operated and maintained.

The B&F budget request is the product of a comprehensive, corporate capital facilities planning process. This process begins with extensive consultation across the research community and the NIH's professional facilities staff. It works through the Facilities Working Group, an advisory committee to the NIH Steering Committee, and the HHS Capital Investment Review Board. Through this process, the program demand for more effective and efficient facilities designed to support current and emerging investigative techniques, technologies, and tools is integrated with, and balanced against, the need to repair, renovate, and improve the existing building stock to keep it in service and to optimize its utility.

The fiscal year 2006 request provides the necessary funding support for the ongoing safety, renovation and repair, and related projects that are vital to proper stewardship of the entire portfolio.

The fiscal year 2006 B&F budget request is organized among three broad Program Activities: Essential Safety and Regulatory Compliance, Repairs and Improvements and Construction. The fiscal year 2006 request provides funds for specific projects in each of the program areas. The projects and programs enumerated are the end result of the aforementioned NIH facilities planning process and are the NIH's capital facility priorities for fiscal year 2006.

FISCAL YEAR 2006 BUDGET SUMMARY

The fiscal year 2006 budget request for Buildings and Facilities is $81.9 million. The B&F request contains a total of $14 million for Essential Safety and Regulatory

Compliance programs composed of $2 million for the phased removal of asbestos from NIH buildings; $5 million for the continuing upgrade of fire and life safety deficiencies of NIH buildings; $1.5 million to systematically remove existing barriers to persons with disabilities from the interior of NIH buildings; $0.5 million to address indoor air quality concerns and requirements at NIH facilities; and $5 million for the continued support of the rehabilitation of animal research facilities. In addition, the fiscal year 2006 request includes $66.9 million in Repairs and Improvements for the continuing program of repairs, improvements, and maintenance that is the vital means of maintaining the complex research facilities infrastructure of the NIH; and $1 million in Construction for pre-project planning including concept development studies and analyses of NIH-wide facility projects proposed in the facilities plan.

My colleagues and I will be happy to respond to any questions you may have.

OFFICE OF AIDS RESEARCH

FISCAL YEAR 2006 NIH AIDS RESEARCH BY-PASS BUDGET ESTIMATE

INTRODUCTION

In its report on the fiscal year 2005 budget for the Department of Health and Human Services, the Senate Committee on Appropriations stated:

"The NIH Office of AIDS Research [OAR] coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Congress provided new authorities to the OAR to fulfill these responsibilities in the NIH Revitalization Action Amendments of 1993. The law mandates the OAR to develop an annual comprehensive plan and budget for all NIH AIDS research and to prepare a Presidential bypass budget." (Senate Report 108–345, page 175)

Public Law 103–43, the National Institutes of Health Revitalization Act of 1993, requires that "the Director of the Office of AIDS Research establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health." It also requires that the Director "shall prepare and submit directly to the President, for review and transmittal to the Congress, a budget estimate for carrying out the Plan for the fiscal year . . ." That budget "shall estimate the amounts necessary for the agencies of the National Institutes of Health to carry out all AIDS activities determined by the Director of the Office to be appropriate, without regard to the probability that such amounts will be appropriated."

In accordance with the law, the Office of AIDS Research (OAR) has developed the fiscal year 2006 Professional Judgment (By-Pass) Budget Estimate for NIH AIDS Research to carry out the scientific priorities of the fiscal year 2006 NIH Plan for HIV-Related Research. This By-Pass budget estimate is based on the following criteria: the commitment to support only the highest quality research; and the urgent need to pursue priority scientific opportunities.

OMB PART

The NIH AIDS program received an overall score of 83 in the 2005 PART. This score included a 100 percent in the Program Purpose and Design section. The human and economic toll of the AIDS pandemic requires a unique response that is complex, comprehensive, multi-disciplinary, and global. The NIH role in this response is unprecedented, comprising a comprehensive program of basic, clinical, and behavioral research on HIV disease to better understand the basic biology of HIV and develop effective therapies and prevention strategies. PART demonstrated that NIH provides effective scientific coordination and management of this diverse AIDS research portfolio through a comprehensive planning and budget development process, which was utilized to develop the fiscal year 2006 By-Pass Budget Request.

OAR COMPREHENSIVE PLAN

The OAR has established a unique and effective model to develop a consensus on the scientific priorities of the annual comprehensive AIDS research plan, called the NIH Plan for HIV-Related Research, that is based on the most compelling scientific priorities that will lead to better therapies and prevention strategies for HIV infection and AIDS. The planning process involves the NIH Institute and Center Directors; NIH intramural and extramural scientists and program managers; scientists and researchers from other government agencies, academia, foundations, and industry; HIV-infected individuals; and other community representatives. The plan also is reviewed by the OAR Advisory Council.

The NIH fiscal year 2006 Plan for HIV-Related Research is divided into five Scientific Areas including: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science. The plan further addresses critical issues that cut across all of the scientific areas: Microbicides; HIV Prevention Research; Racial and Ethnic Minorities; Women and Girls; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination.

The fiscal year 2006 NIH AIDS research agenda continues the following overarching themes: a strong foundation of basic science; HIV prevention research, including development of vaccines, microbicides, behavioral interventions, and strategies to prevent perinatal transmissions; therapeutics research to develop simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated illnesses, malignancies, and other complications; international research, particularly to address the crucial research and training needs in developing countries; and research targeting the disproportionate impact of the AIDS epidemic on racial and ethnic minority populations in the United States.

The Plan shapes NIH investments in biomedical and behavioral AIDS research and provides the framework to translate critical research findings to benefit populations desperately in need both in our country and abroad. The Plan serves as the framework for developing the annual NIH AIDS research budget; for determining the use of NIH AIDS-designated funds; for tracking and monitoring AIDS-related expenditures; and for informing the scientific community, the public, and the AIDS-affected community about NIH AIDS research priorities. The entire plan can be found on the OAR web site: http://www.nih.gov/od/oar/public/pubs/fy2006/00__Overview__fiscal year 2006.pdf

OAR BUDGET DEVELOPMENT PROCESS

The Plan initiates the budget development process. Based on the objectives and priorities established in the Plan, the NIH Institutes and Centers (ICs) prepare their AIDS research budget requests, detailing new or expanded program initiatives for each scientific area. The OAR reviews the IC initiatives in relation to the Plan, to OAR priorities, and to other IC submissions to eliminate redundancy and/or to assure cross-institute collaboration. The OAR allocates the AIDS research budget levels to each IC based on the scientific priority of the proposed initiatives.

This process allows the OAR to ensure that AIDS research funds will be provided to the most compelling scientific opportunities, rather than distribution based solely on a formula.

OAR BY-PASS BUDGET PRIORITIES

The fiscal year 2006 NIH By-Pass Budget for HIV/AIDS Research responds to several crucial scientific opportunities and needs. In fiscal year 2005, OAR initiated a comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds to ensure that these projects represent the highest scientific priorities and opportunities. This process also included: (1) a review of the appropriateness of definitions of HIV/AIDS research in the institutes (i.e., coding of research as AIDS or AIDS-related) and the mix of investments in key priority areas in view of the current epidemic; and (2) a series of meetings with IC representatives to assess their AIDS portfolios relative to AIDS and AIDS-related priorities. This process will result in the redirecting of AIDS funds to higher priority projects and new scientific opportunities in fiscal year 2006.

NIH-sponsored HIV/AIDS research continues to provide the important scientific foundation necessary to design, develop, and evaluate new and better vaccine candidates, therapeutic agents and regimens, and prevention interventions. In particular, this By-Pass budget places a renewed priority on the discovery, development, and pre-clinical testing of additional HIV vaccine candidates. The NIH priority in AIDS vaccine research to date has resulted in approximately 70 clinical trials of nearly 40 vaccine candidates. The evaluation of an AIDS vaccine will require extensive testing in the United States and in international settings where there is a high incidence of HIV. High priority is placed in this budget on funding to move promising vaccine candidates into large-scale clinical trials to evaluate the potential for efficacy.

In the area of AIDS therapeutics research, current therapeutic regimens have resulted in extended survival and improved quality of life for many HIV-infected individuals in the United States and Western Europe. However, a growing proportion of patients receiving therapy are demonstrating treatment failure, experiencing serious drug toxicities and side effects, and developing drug resistance. This By-Pass budget provides critical support for the development of new and better drugs using

sophisticated structural biology, combinatorial chemistry, and macromolecular techniques. The goal of this research is to develop new, safe, less toxic, less expensive, and more effective therapeutic agents and regimens.

The increasing incidence of metabolic disorders, cardiovascular complications, major organ dysfunction, and physical changes associated with current antiretroviral drugs underscores the critical need for new and better treatment regimens. Improved regimens also are needed to treat HIV co-infections such as hepatitis B and C, as well as other opportunistic infections to reduce drug interactions and problems with adherence to complicated treatment regimens.

In fiscal year 2005, the Office of AIDS Research spearheaded a critical and unique multi-IC inter-disciplinary collaboration to formalize plans for the innovative restructuring of the NIH clinical trials networks for HIV therapeutics, vaccines and prevention interventions in fiscal year 2006. OAR convened meetings of relevant IC high-level staff, established an OAR Working Group of United States and international clinical trialists, and convened a public meeting of over 145 participants from universities, medical schools, the pharmaceutical and biotechnology industries, professional scientific societies, community advisory boards, constituency groups, and NIH IC program staff to develop a set of principles to guide the development of Request For Application (RFAs) for these multi-IC supported clinical programs. This effort made a significant contribution to the process of the recompetition of these networks in fiscal year 2006 and to ensuring that they will operate effectively and cooperatively, making the best use of research funds.

The alarming continued spread of the pandemic in Southeast and Central Asia, Eastern Europe, Latin America, and the Caribbean underscores the urgent need for more affordable and sustainable prevention and treatment approaches that can be implemented in resource-limited nations. The high incidence of Hepatitis B and Hepatitis C, malaria, and TB in many of these nations further complicates the treatment and clinical management of HIV-infected individuals. This budget provides increased funds for the development and evaluation of new regimens for these HIV co-infections that will allow the treatment of these diseases without serious drug interactions and toxicities.

The By-Pass budget provides funds for NIH international AIDS research including: HIV vaccine candidates and chemical and physical barrier methods, such as microbicides, to prevent sexual transmission; behavioral strategies targeted to the individual, family, and community to alter risk behaviors associated with sexual activity and drug and alcohol use; drug and non-drug strategies to prevent mother-to-child transmission (MTCT); therapeutics for HIV-related co-infections and other conditions; and approaches to using Antiretroviral Therapy (ART) in resource-poor settings. Specific international infrastructure needs include: (1) developing research sites through establishment of stable, targeted cohorts, development of recruitment strategies, and enhancement of laboratory, clinical, and data management capabilities; (2) increasing the number of scientists, clinicians, and health care workers trained in basic, clinical, and behavioral research, data management, and ethical considerations; (3) developing research collaborations; and (4) transferring appropriate clinical and laboratory technologies.

OAR BY-PASS BUDGET ESTIMATE

NIH is enhancing collaboration, minimizing duplication, and ensuring that research dollars are invested in the highest priority areas of scientific opportunity that will allow NIH to meet its scientific goals.

The total fiscal year 2006 By-Pass budget estimate for all NIH AIDS research is $3.387 billion. This represents an increase of $442 million or 15 percent over the fiscal year 2005 current estimate of $2.945 billion.

The NIH Office of AIDS Research is providing the following materials: NIH fiscal year 2006 Plan for HIV-Related Research; NIH Research Mechanism Table; and Table of Funding by the NIH fiscal year 2006 Plan for HIV-Related Research.

ATTACHMENT 1.—OFFICE OF AIDS RESEARCH FISCAL YEAR 2006 BY-PASS SUMMARY MECHANISM

[Dollars in millions]

	Fiscal years							
	2004 estimate		2005 estimate		2006 by-pass		2006 over 2005 dollar change	
	No.	Amount	No.	Amount	No.	Amount	Percent	Amount
Research Projects:								
Noncompeting	2,245	$1,173	2,407	$1,268	2,370	$1,087	−14.3	−$181
Administrative supplements	(14)	18	(16)	19	(20)	17	−10.5	−2
Competing	1,035	376	804	307	1,178	712	131.9	405
Subtotal, RPGs	3,266	1,567	3,195	1,594	3,528	1,816	13.9	222
SBIR/STTR	91	31	103	35	105	41	17.1	6
Total, RPGs	3,357	1,598	3,298	1,629	3,633	1,857	14.0	228
Research Centers:								
Specialized/comprehensive	61	104	61	111	63	120	8.1	9
Clinical research	.....	43	.....	45	.....	49	8.9	4
Biotechnology	.....	6	1	7	.....	7	.....	.....
Comparative medicine	17	48	17	52	17	65	25.0	13
Research centers in minority institutions	.....	10	.....	10	.....	11	10.0	1
Subtotal, Centers	78	211	79	225	80	252	.....	27
Other Research:								
Research careers	235	30	240	31	235	34	9.7	3
Cancer education	.....	.....	.....	.....	.....	.....	.....	.....
Cooperative clinical research	25	44	25	44	25	44	.....	.....
Biomedical research support	1	2	1	2	1	3	50.0	1
Minority biomedical research support	2	1	2	1	3	1	.....	.....
Other	115	62	114	64	115	72	12.5	8
Subtotal, Other Research	378	139	382	142	379	154	.....	12
Total, Research Grants	3,813	1,948	3,759	1,996	4,092	2,263	.....	.....
FTTPs								
Training:								
Individual	62	3	62	3	62	3	.....	.....
Institutional	703	31	723	32	737	33	3.1	1
Total, Training	765	34	785	35	799	36	2.9	1
Research & development contracts	181	364	190	415	225	553	33.3	138
(SBIR/STTR)	(10)	(2)	(10)	(2)	(10)	(1)	−50.0	(1)
Intramural research	.....	325	.....	331	.....	356	7.6	25
Research management and support	.....	96	.....	99	.....	106	7.1	7
Construction	.....	5	.....	.....	.....	.....	.....	.....
Library of Medicine	.....	7	.....	8	.....	10	25.0	2
Office of the Director	.....	61	.....	61	.....	63	3.3	2
Buildings and Facilities	.....	.....	.....	.....	.....	.....	.....	.....
Total, Budget Authority	.....	2,840	.....	2,945	.....	3,387	15.0	442

ATTACHMENT 2.—OFFICE OF AIDS RESEARCH, FISCAL YEAR 2006 BY-PASS, FUNDING BY THE NIH PLAN FOR HIV-RELATED RESEARCH

[Dollars in millions]

	Fiscal year							
						2006 over 2005		
	2002 actual	2003 actual	2004 estimate	2005 estimate	2006 by-pass	Dollar change	Percent of increment	Percent change
Natural History and Epidemiology	$276	$295	$293	$296	$315	$19	4.3	6.4
Etiology and Pathogenesis	685	727	716	728	812	84	19.0	11.5
Therapeutics	689	726	754	771	848	77	17.4	10.0
Vaccines	329	407	467	529	714	185	41.9	35.0
Behavioral and Social Science	346	370	402	408	457	49	11.1	12.0
Training and Infrastructure	121	137	165	169	191	22	5.0	13.0
Information Dissemination	53	55	43	44	50	6	1.4	13.6
Total	2,499	2,717	2,840	2,945	3,387	442	100	15.0

PREPARED STATEMENT OF DR. ANTHONY S. FAUCI

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The fiscal year 2006 budget of $4,459,395,000 includes an increase of $56,554,000 over the fiscal year 2005 enacted level of $4,402,841,000, comparable for transfers proposed in the President's request.

NIAID conducts research to understand, treat, and prevent infectious and immune-related diseases. Infectious diseases include well-known killers such as tuberculosis and malaria, emerging or re-emerging threats such as HIV/AIDS, SARS, West Nile Virus and influenza, and "deliberately emerging" threats from potential agents of bioterrorism such as those that cause anthrax and smallpox. Examples of immune-related diseases include autoimmune disorders such as type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, transplantation-related illnesses, asthma, and allergies.

Historically, NIAID has accomplished its mission with a strong commitment to basic and targeted research in immunology, microbiology, and infectious disease. In the 57 years since NIAID was founded, this approach has led directly to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people worldwide. In recent years, however, the growing realization that the nation needs a stronger defense against both naturally and deliberately emerging infectious diseases has led NIAID to adopt a new research paradigm that accelerates the development of safe and effective medical countermeasures. To accomplish this, we have sought creative ways to modify our traditional process of research and development to move potential products ahead more rapidly while continuing to preserve the excellence in basic research that is a hallmark of NIAID, and all of NIH. The result is that we now take a much more proactive role in collaborating with academia, industry and other partners to move promising concepts into advanced product development and clinical testing.

BIODEFENSE RESEARCH

In the wake of the 2001 terrorist attacks, NIAID substantially expanded and accelerated its biodefense research program. The fiscal year 2006 President's budget request for NIAID includes $1,664,505,000 for these biodefense research and development activities. The NIAID Strategic Plan for Biodefense Research provides a blueprint for the construction of three essential pillars of the NIAID biodefense research program: infrastructure needed to safely conduct research on dangerous pathogens ($30,000,000 in fiscal year 2006); basic research on microbes and host immune defenses that serves as the foundation for applied research ($612,190,000 in fiscal year 2006); and targeted, milestone-driven research and development of medical countermeasures to create the vaccines, therapeutics and diagnostics that we would need in the event of a bioterror attack ($1,022,315,000 in fiscal year 2006).

The investment Congress has made in the NIAID biodefense research program has already begun to return substantial dividends in all three of these aspects of

biodefense research. Dramatic advances have been achieved in the development of medical countermeasures against an attack with biological agents, and, although there is much more to be accomplished, we are in a far stronger position today than we were only a few years ago. In September 2001, we had 15.4 million doses of smallpox vaccine available; today, we have more than 300 million doses. A next-generation smallpox vaccine called modified vaccinia Ankara (MVA) is in clinical testing and other vaccine candidates are in pre-clinical development stages. A new oral form of the antiviral drug cidofovir is in advanced product development for use in the event of a smallpox attack, as well as to treat the rare but serious complications of the classic smallpox vaccine. For anthrax, NIAID has aggressively pursued development of a new vaccine called rPA; the Department of Health and Human Services (DHHS) has contracted with VaxGen, Inc. to purchase 75 million doses of rPA under the BioShield legislation passed last year. This vaccine is derived using molecular biological methodologies and is produced using modern vaccine manufacturing techniques and may require fewer doses than the currently licensed vaccine. New anthrax therapies that can neutralize the anthrax toxin, such as monoclonal and polyclonal antibodies, are being developed. Candidate antibody treatments for the toxin that causes botulism are in development, as is a new vaccine to prevent the disease. Finally, an Ebola recombinant DNA vaccine is in initial human clinical trials at the NIAID Vaccine Research Center.

With regard to research infrastructure, many integrated research facilities are under construction to safely contain and study pathogens, including several new biodefense laboratories that will be owned and operated by NIAID. In addition, sites have been selected for the construction of two National Biocontainment Laboratories (NBLs) and nine Regional Biocontainment Laboratories (RBLs) at major universities around the United States. All of these research laboratories will provide the secure facilities needed to carry out the nation's expanded biodefense research program in settings that protect workers and the surrounding communities. NIAID also has funded eight Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). This nationwide network of multidisciplinary academic centers will conduct wide-ranging research to better understand infectious agents that could be used in bioterrorism, and will develop diagnostics, therapeutics and vaccines needed for biodefense against these agents. In 2005, NIAID will fund two additional RCEs and three to four additional RBLs. NIAID also has developed and expanded contracts to screen new drugs against bioterrorism threat agents, developed new animal models for bioterrorism threat agents, and established a biodefense reagent and specimen repository.

Advances in Medicine rest on a foundation of basic research into the fundamental properties and mechanisms of life. In biodefense, these basic studies include sequencing and understanding of microbial genomes (genomics) and their products (proteomics), deciphering how microbes cause disease (pathogenesis), and examining how the human immune system and pathogens interact (immunology). NIAID-funded basic researchers have made significant progress since 2001 in each of these areas. For example, researchers have now determined the genetic sequence of at least one strain of every pathogen identified as a potential bioterror threat, and NIAID has established the Pathogen Functional Genomics Resource Center to help researchers apply and analyze these new genome sequence data. In pathogenesis, NIH researchers recently determined the three-dimensional structure of the anthrax toxin bound tightly to a target cell surface receptor. This finding has provided new leads for the development of novel antitoxins that could save lives late in the course of anthrax disease when large amounts of toxin are present and antibiotics alone are no longer sufficient to save the patient. Finally, basic molecular and cellular studies of the human innate immune system, which is comprised of broadly active "first responder" cells and other mechanisms that are the first line of defense against infection, have been moving forward rapidly. These advances suggest it may be possible to develop fast-acting countermeasures that boost innate immune responses to mitigate the effects of a broad spectrum of bioterror pathogens or toxins. Manipulation of the innate immune system also could lead to the development of powerful adjuvants that can be used to increase the effectiveness of vaccines.

The knowledge and products that will flow from the NIAID biodefense research program, including research results, intellectual capital, laboratory resources, and countermeasures in the form of diagnostics, therapeutics, and vaccines, will help us cope with naturally emerging, re-emerging, and deliberately released microbes alike. Recent experience tells us that knowledge developed to understand one pathogen invariably applies to others. For example, when HIV first emerged, antiviral drug development was in its infancy. Now, new technologies have led to the development of more than 20 antiretroviral drugs that can effectively suppress HIV replication and dramatically reduce AIDS morbidity and mortality. These same technologies,

and the lessons learned about antiviral drug development, are being applied to the development of new generations of drugs against many viruses, including influenza, SARS, smallpox, and Ebola. Even if we are never confronted with another bioterror attack, the biodefense research and preparations being carried out now will without question prove to be very valuable.

HIV/AIDS RESEARCH

Only a few statistics are needed to present a profoundly disturbing picture of the still-emerging HIV/AIDS pandemic. Approximately 40 million people worldwide are living with HIV/AIDS, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS). Every year, more than 5 million people worldwide are newly infected with the virus—about 14,000 each day; more than 95 percent of these people live in low and middle income countries. In the United States, nearly one million people are living with HIV/AIDS, and approximately 40,000 new infections occur annually, according to the Centers for Disease Control and Prevention. The death toll continues to climb steadily; worldwide, more than 20 million people with HIV have died since the pandemic began, including more than 520,000 in the United States. In 2004, there were 3 million deaths due to HIV/AIDS. As shocking as these numbers are, they do not adequately communicate the physical and emotional devastation to individuals, families, and communities coping with HIV/AIDS, nor do they capture the terrible impact of HIV/AIDS on the economies and security of nations, and indeed on entire regions.

Even as the burden of HIV/AIDS continues to grow, recent progress in research is providing reasons for optimism. For example, several new antiretroviral drugs recently have entered the market, all of which were built on NIAID-sponsored research and/or were tested in NIAID clinical trials networks; many other new anti-HIV drugs are in clinical trials. Other novel approaches to anti-HIV drugs are in the research "pipeline." For example, NIAID scientists, in collaboration with extramural colleagues and with industry, recently conducted a clinical trial to test a product, anti-CCR5, that binds to a new therapeutic target, the HIV co-receptor, thus preventing HIV infection of host cells.

The development of a safe and effective HIV vaccine is one of NIAID's highest priorities. The scientific barriers to the creation of such a vaccine are extraordinarily high, and better coordination, collaboration and transparency of research worldwide would help to overcome them. To facilitate such an approach, NIAID participated heavily in the creation of a new initiative called the Global HIV/AIDS Vaccine Enterprise, which was endorsed by President Bush and the other G8 countries at their June, 2004 Summit meeting in Sea Island, GA. The project creates a worldwide consortium of people and organizations with a stake in HIV vaccine research who agree to harmonize their individual HIV vaccine efforts by following a unified Strategic Plan for HIV vaccine development. This plan was published on a publicly-accessible website in February 2005.

Other measures to prevent HIV transmission also are being vigorously pursued. For example, when I testified here last year I discussed our efforts to develop topically applied microbicides that women could use to protect themselves from HIV and other sexually transmitted pathogens. More than 50 candidate agents have shown activity against HIV and other sexually transmitted diseases in the laboratory, and several of these have been shown to be safe and effective in animal models. In February 2005, a large international study, sponsored by NIAID and involving more than 3,000 women at high risk of acquiring HIV in the United States and five African countries, opened for enrollment. If these microbicides are proven to be safe and effective, they likely will become a very important means of slowing the pace of the HIV/AIDS epidemic.

RESEARCH ON OTHER EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Infectious diseases do not remain static, but continually and dramatically change over time. New pathogens, such as the Severe Acute Respiratory Syndrome (SARS) coronavirus, can emerge suddenly and familiar ones, such as influenza virus and West Nile virus, can re-emerge with new properties or in unfamiliar settings. We must always be on guard for such changes and be prepared to react to them as quickly as possible. SARS is a prototypical example of a newly-emerging infectious disease. When SARS first came to the world's attention in early 2003 as an unknown, highly lethal and transmissible disease, researchers and public health authorities the world over immediately began to collaborate to understand it. In short order, NIAID-supported researchers and others in Hong Kong showed that SARS was caused by a previously unrecognized coronavirus, epidemiologists unraveled its

modes of transmission, and public health authorities were able to contain the initial outbreak.

Since then, NIAID has continued to pursue several approaches to the development of SARS antiviral therapies. For example, NIAID screening contracts have supported the evaluation of more than 20,000 chemicals for anti-SARS coronavirus activity. More than 1,400 compounds with activity against SARS coronavirus have been identified, including alpha interferon, a drug already approved by the FDA for the treatment of hepatitis B and C infections.

NIAID scientists and grantees also are working on several approaches to a SARS vaccine, including one that entered human clinical testing in December 2004. It is truly remarkable that two years ago we were facing an unknown global health threat, and now we are already testing a promising vaccine that may help us to counter that threat should it re-emerge.

When West Nile virus (WNV) first appeared in the Western hemisphere in 1999, NIAID immediately increased its basic research on the virus and undertook the development of new vaccines and treatments for the disease. NIAID currently supports the development of three types of WNV vaccine—one of which has entered initial clinical testing—and is developing candidate WNV therapies. For example, in 2004, NIAID expanded an ongoing clinical study in human volunteers that is evaluating the safety and efficacy of the administration of antibodies against the virus as a means of treating or preventing West Nile virus encephalitis.

Influenza is a classic example of a re-emerging disease. Because the influenza virus continually changes, the U.S. influenza vaccine supply must be renewed each year. Although the egg-based technology currently in use has served us reasonably well for more than 40 years, it has limitations in flexibility in that surges in the need for additional or new vaccines cannot be readily accommodated due to the advance time that is required to provide for the annual requirement for hundreds of millions of fertilized chicken eggs to manufacture the vaccine. In addition, there is the ever present risk of contamination and the vicissitudes of yield of virus from this technique. The serious vaccine shortage that occurred this flu season underscores the difficulties we face in annually renewing the influenza vaccine supply, and highlights the pressing need to move toward adoption of newer vaccine manufacturing techniques to improve the flexibility and speed with which vaccines can be made.

NIAID supports several research projects and other initiatives intended to foster the development of new influenza vaccines and manufacturing methods that are simpler and more reliable, yield products that work against multiple influenza strains, and provide greater protection. DHHS has requested $120 million in fiscal year 2006 to help shift vaccine manufacture toward new cell-culture technologies, new production technologies, as well as to provide for year-round availability of eggs to provide for a secure supply and surge capacity. In addition, a technique developed by NIAID-supported scientists called reverse genetics allows scientists to manipulate the genomes of influenza viruses to make the process of development of seed viruses for vaccines faster and more predictable.

Although the impact of influenza in a normal epidemic year is substantial, influenza viruses from animals occasionally cross into humans and, if the virus then acquires the ability to be easily transmitted between people, can cause a much more serious influenza pandemic. NIAID conducts a great deal of research to understand the viral biology and epidemiology that underpinned past pandemics and funds surveillance activities in Asia to detect the emergence of influenza viruses with pandemic potential. In addition, the DHHS draft Pandemic Influenza Response and Preparedness Plan directs NIAID to help develop and produce an effective vaccine as rapidly as possible that could be used should a pandemic alert be declared.

In recent years, avian influenza virus strains that can infect humans have emerged; the most worrisome are known as H9N2 and H5N1. In 1999 and 2003, an H9N2 influenza strain caused illness in people in Hong Kong. The H5N1 "bird flu" influenza strain was first detected in 1997 and has spread widely among wild and domestic birds. This latter virus has infected at least 55 people and killed 42 since January 2004, and there has been at least one documented case of human-to-human transmission.

NIAID has taken several steps to develop vaccines against both of these potential pandemic strains. NIAID contracted with Chiron Corporation to produce investigational batches of an inactivated H9N2 vaccine, which will be evaluated clinically by NIAID this year. For H5N1, Aventis-Pasteur, Inc. and Chiron are both producing investigational lots of inactivated H5N1 vaccine preparations; additionally, DHHS has contracted with Aventis to produce up to 2 million doses to be stockpiled for emergency use, if needed, to vaccinate health workers, researchers, and, if indicated,

the public in affected areas. Development and evaluation of a combination antiviral regimen against these potential pandemic influenza strains are also now under way.

RESEARCH ON IMMUNE-MEDIATED DISEASES

Immune-mediated diseases, including autoimmune diseases, allergic diseases, and asthma are important health challenges in the United States and abroad. One of the most promising strategies for developing treatments for a wide variety of these disorders is known as immune tolerance, in which researchers hope to selectively turn off injurious immune responses while leaving intact the protective responses needed to fight infection. To foster this research, NIAID sponsors the Immune Tolerance Network (ITN), a consortium of more than 80 investigators in the United States, Canada, Western Europe, and Australia dedicated to the clinical evaluation of promising therapies that can induce immune tolerance. The ITN will be recompeted in fiscal year 2006.

Reducing the growing burden of asthma among inner-city minority children is another NIAID priority. NIAID-supported investigators recently reported the largest study of its kind, showing that an intervention to reduce exposure to indoor allergens and tobacco smoke substantially reduced asthma severity and healthcare utilization among inner-city children. In 2004, NIAID's Inner-City Asthma Consortium launched a large study to define and analyze immunological and environmental influences upon the development of childhood asthma in a cohort of urban children followed from birth.

In closing, Mr. Chairman, I would like to take a moment to remember John R. La Montagne, Ph.D., the former deputy director of NIAID, who died suddenly on November 2 while traveling to a meeting of the Pan American Health Organization in Mexico City. Human infrastructure, in the form of a highly trained and deeply committed work force, is a critical component of any kind of medical research. Throughout John's almost 30 years at NIAID, his leadership and dedication to improving global health, as well as his generosity, wit, even-handedness and kindness, made him a cornerstone of the human infrastructure at NIAID. Personally, he was a dear friend and one of the finest people I have ever known. He is sorely missed.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee might have.

PREPARED STATEMENT OF DR. ANDREW C. VON ESCHENBACH

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Cancer Institute (NCI) for fiscal year 2006. The fiscal year 2006 budget includes $4,841,774,000, an increase of $16,516,000 over the fiscal year 2005 enacted level of $4,825,258,000 comparable for transfers proposed in the President's request.

LONG-TERM GOAL

The accelerating progress that the National Cancer Institute (NCI) and its partners in the cancer community have made over the past three decades in understanding the molecular mysteries of cancer is now extending the years and enhancing the quality of patients' lives. Now we are closer to the reality of eliminating the suffering and death due to cancer—the goal that NCI set to be achieved by 2015. The fiscal year 2006 budget continues to accelerate the discovery, development, and delivery of the interventions that will transform our traditional view of cancer as a death sentence into a disease that we can prevent, eliminate, or control. Accomplishing this goal is the legacy we strive to leave our children.

Our increased knowledge in several clinical approaches has led to new treatments approved for use. For example, our understanding of the molecular mechanisms required for tumors to develop the blood supply necessary for their growth led to the Food and Drug Administration's (FDA) approval of the monoclonal antibody Avastin® as a first-line treatment for patients with metastatic colorectal cancer. Similarly, knowledge of the growth factors necessary to stimulate cancer cell proliferation led to development and approval of another targeted monoclonal antibody Erbitux® for the treatment of metastatic colorectal carcinoma and to the accelerated approval of Alimta® for locally advanced or metastatic non-small cell lung cancer. These are just a few of the new drugs offering fresh hope for patients with advanced cancer.

We have made progress in preventing cancer from ever developing in the first place, especially in people at high risk. An example is the creation of a vaccine that

has prevented women from becoming persistently infected with human papilloma viruses (HPV), an infection that is responsible for half of all cervical cancers.

Now we must quicken the pace of progress because the trajectory is clear: discovery of cancer's genetic and molecular mechanisms leads to development of innovative interventions that—when delivered to patients—save lives. Building on this knowledge, the promise of tomorrow's advances is just over the horizon. This hopeful prospect will be realized by investing in strategic research areas, including: cancer genomics, biomarkers, molecular imaging, nanotechnology, and bioinformatics.

ADVANCED TECHNOLOGY INITIATIVES

The technology revolution is speeding up and enabling the discovery process. Recent advances in molecularly-targeted imaging will allow us to locate very small tumors and interrogate their features. Nanotechnology has emerged as a key strategy for imaging molecular features of cancer that are notoriously difficult to detect. In one case, a team of NCI-supported scientists has crafted a nano-sized device—less than 1/80,000 the width of a human hair—to identify areas of new blood vessel growth, which is characteristic of growing tumors. Further, drugs attached to agents that seek out the proteins on cancer cells will target therapy to exactly where it is needed without damage to healthy cells.

The development, integration, and coordination of advanced technologies are pivotal to enabling the biomedical and cancer research advances that are necessary to achieve NCI's 2015 goal. The Institute has played a crucial role in charting the path and collaborating in efforts to support bold new programs in this crucial arena.

For instance, the National Advanced Technologies Initiative for cancer (NATIc) is a plan to create a nationwide "virtual" laboratory for cancer. The NATIc plan envisions a network of state and regional technology "hubs" focused on several strategic areas, including advanced computing, nanotechnology, and biorepositories.

NCI has already begun development of the cancer Biomedical Informatics Grid (caBIG) to create a "world-wide web" for cancer research. The goal is to create a network of interconnected data, applications, individuals, and institutions that will redefine how cancer research is conducted and care is provided. During its initial year, the caBIG enterprise began bearing its first fruits with the release of NCI's caArray, a prototype software application that is made freely available to facilitate the sharing and analysis of microarray data by the medical research community. NCI and its partners in academia and industry are also developing an online information infrastructure to support clinical trials management and electronic drug approval submissions to the FDA. The first system module—the Federal Investigator Registry (Firebird)—starts pilot testing this spring.

In addition, NCI has for the first time adopted a modern business model approach to our research and development program for cancer-imaging technologies. This entailed creation of an Imaging Integration/Implementation (I^2) Team that recently submitted a proposed business plan for a new entity to be called I^2 Imaging, Inc. The goal is to create distinct product lines to organize NCI's imaging program and clearly define measurable goals for each of the product lines. The plan includes four R&D programs encompassing imaging technologies for: (a) understanding of cancer biology and microenvironments; (b) cancer prevention and preemption; (c) development and preclinical validation of therapies; and (d) tools for clinical trial support.

STRATEGIC RESEARCH INITIATIVES

Exponential advances in cancer research are defining, with ever increasing specificity, the many genetic, molecular, and cellular events that influence the cancer process. We now understand cancer as an ongoing process that can be interrupted at many stages—from susceptibility to initiation to disease progression. We are translating this new knowledge into innovative strategies to prevent cancer from developing, eliminate it early when it does occur, and modulate its devastating effects. This involves NCI making strategic investments in several research areas.

Cancer prevention, early detection, and prediction.—New evidence-based interventions encourage lifestyle improvements in diet and physical activity, discourage tobacco use, and promote safe and fully-tested chemoprevention approaches for people at risk. Pioneering proteomic and biomarker advances, and the promise of nanotechnology, give us new hope for the early detection of cancer and prediction of patient responses to treatment.

Development of strategic cancer interventions.—One of NCI's key strategies is to optimize the development and speed delivery of targeted cancer diagnostics, therapies, and preventives to patients. This is evidenced by NCI's investments into the Cancer Genome Anatomy Project, Academic Public-Private Partnership programs, and Rapid Access to Intervention Development (RAID).

An integrated clinical trials system.—NCI provides leadership, resources, and expertise for clinical trials programs that span the discovery of novel molecules to the evaluation of new agents and interventions. To make clinical trials more efficient and to accelerate and improve the regulatory approval process, NCI is enhancing its working relationship with the FDA and the Department of Health and Human Services' (DHHS) Office of Human Research Protections to develop more streamlined policies and procedures for the conduct of clinical trials.

Integrative cancer biology.—Integrative cancer biology is the study of cancer as a complex biological system. NCI's initiatives in this cutting-edge area include creating computational models of the complex networks within and among cancer cells, building our understanding of the tumor microenvironment, and studying the role of the tumor macroenvironment in cancer development.

Molecular epidemiology.—NCI is developing novel ways to unravel the complexities of inherited and environmental contributions to cancer causation. Future investments will help scientists uncover risk factors, identify genetically susceptible individuals, and generate individual and public health strategies to avoid or mitigate adverse genetic exposures.

INTERAGENCY COLLABORATIONS

Cancer is a large and complex problem with scientific, medical, social, cultural, and economic dimensions. Addressing this problem requires that NCI work across institutional and sector boundaries, share knowledge, and bring together the diverse members of the DHHS family of agencies, as well as other Federal offices, that can help develop systems-based solutions to the cancer problem. Just within the National Institutes of Health (NIH), NCI collaborates with virtually all of the 27 Institutes and Centers. Likewise, NCI also has many ongoing collaborations with several DHHS agencies. The ultimate beneficiaries of this continued cooperative effort will be cancer patients and their families.

NCI and FDA created an Interagency Oncology Task Force (IOTF) to remove bottlenecks in the process of developing and approving safe, more effective cancer interventions. IOTF, which is comprised of senior representatives from both agencies, has been meeting regularly to define key areas of mutual interest and concern. As a result, the NCI-FDA Cancer Training Fellowship Program was launched in 2005. The program will train a cadre of scientists in research and research-related regulatory review so that they can develop skill sets that bridge the two distinct processes.

NCI is also an active participant in the Medical Innovation Task Force established last year by DHHS. The group—which also includes the FDA, the Centers for Disease Control and Prevention, the Centers for Medicare & Medicaid Services, and the NIH—is weighing new ideas and solutions to encourage innovation in health care. The interagency panel seeks to speed the delivery to market of effective new medical technologies, such as drugs, biological products, and medical devices.

NIH ROADMAP

NCI's contributions to NIH Roadmap initiatives will increase NCI's ability to support the collaborative research critical to cancer studies. Cooperation across the cancer continuum is vital for continued progress. The NIH Roadmap mechanisms support research in cancer biology that will also enhance continued interdisciplinary research to address vital questions related to cancer and the immune system, the interface of aging and cancer, and the role of microbial agents in the etiology of human cancers. By encouraging interdisciplinary teams to evolve in both directed and serendipitous ways, these new funding mechanisms complement and enlarge NCI's efforts toward the integration and cross-fertilization of research efforts that span the cancer spectrum.

CHALLENGES AND OPPORTUNITIES

In the coming years, we will face a number of critical challenges and opportunities. We stand on the brink of a new age of "personalized oncology"—delivering the right treatment to the right patient at the right time to halt cancer-causing processes in the body before they cascade into advanced disease states. NCI is driven to meet the 2015 challenge goal. Cancer is a public health and financial challenge for the United States. NIH estimates that in 2003, the total cost of cancer was over $189 billion: $64 billion in direct medical costs (much of it paid by Medicare) and $125 billion from lost productivity due to illness and premature death. More telling, 570,000 Americans lost their lives to the disease last year, according to the American Cancer Society. Furthermore, the fact that cancer occurs primarily in individuals over the age of 50 means that more of our citizens will suffer the terrible bur-

den of this disease in the future due to the aging and changing demographics of our population. NCI and its partners are committed to making progress toward the goal of eliminating suffering and death due to cancer in the next 10 years.

Thank you, Mr. Chairman. I would be pleased to answer any question that the Committee may have.

PREPARED STATEMENT OF DR. BARBARA ALVING, ACTING DIRECTOR, NATIONAL CENTER FOR RESEARCH RESOURCES

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Center for Research Resources (NCRR) for fiscal year 2006, a sum of $1,100,203,000, which reflects a net decrease of $14,887,000 over the comparable fiscal year 2005 appropriation. Within the total is $162,618,000 for AIDS research.

I am delighted to have this opportunity to share with you the scientific advances achieved by NCRR-supported investigators and the future directions for NCRR programs. As the "research resources" component of the National Institutes of Health, NCRR's mission is to ensure that scientists have the necessary tools and access to research environments to conduct their progressively more complex research on human disease. With ready access to essential tools, our nation's top scientists may creatively explore promising new research avenues that will ultimately enhance human health.

Because of its cross-disciplinary programs, NCRR supports research tools and infrastructure that enable all lines of biomedical inquiry, from studies of molecular structures to clinical trials that evaluate potential therapies. Most NCRR-supported research resources are shared and accessible to scientists nationwide. These shared resources include advanced instrumentation and novel technologies, animal models of human disease, and electronic networks for collaborations among investigators in less populated areas. In addition, through the Institutional Development Award program, NCRR provides support to institutions in 23 states and Puerto Rico to develop new research facilities, equipped with state-of-the art research tools.

NCRR encourages resource sharing because it broadens access to essential tools, is cost effective, and leverages precious federal research support. Each year, NCRR-funded research resources are used by more than 35,000 investigators who receive their primary research support from other NIH components, other federal agencies, and the private sector. Let me briefly describe just a few of the science advances that these researchers achieved over the past year.

OBESITY STUDIES AIDED BY ANIMAL AND CLINICAL RESOURCES

Scientists who seek to determine the genetic defects of many human diseases are often stymied by the fact that common conditions—from obesity to psychiatric disorders—are influenced by multiple genes. Therefore, researchers have turned to inbred mice as a model system for detecting genetic regions that contribute to complex disease. Using unique mouse strains available through an NCRR resource, scientists examined genetic factors that affect many complex traits, including obesity and anxiety. With this approach about 150 previously undiscovered genetic regions were discovered. This effort may narrow the search for specific genes that contribute to obesity and also pave the way for finding similar genes in humans.

NCRR's General Clinical Research Centers (GCRCs) provide an ideal research environment for studies of obesity, an increasing public health concern. Particularly valuable are the GCRCs' highly trained staff and state-of-the-art equipment that can analyze a patient's metabolism and track consumption of all foods, down to the level of micronutrients. At the University of California, Los Angeles, researchers depend on the GCRC for their carefully controlled studies of the hormones that affect appetite and metabolism. One study found that injections of the hormone leptin can reduce body weight by more than 50 percent in obese individuals born with leptin deficiency. At Yale University's GCRC, scientists evaluated hundreds of overweight children and adolescents and found that about half of the severely obese have a condition that raises their risk of heart disease and type 2 diabetes. Ultimately, better understanding of the risk factors and potential therapies for obesity could lead to a leaner, healthier population.

ADVANCES IN TRANSPLANTATION RESEARCH

As mentioned earlier, the GCRCs continue to have a significant role for advancing human health. For instance, the GCRCs enabled pioneering clinical studies related to transplantation, from the earliest successes with organ transplants in the 1960s

to the current microtransplants of genes into cells. One recent success, reported in the *Journal of the American Medical Association* this past February, showed that islet cells from a single human pancreas can be transplanted into up to eight patients with type 1 diabetes, a condition in which the pancreatic islet cells do not make insulin. All eight transplant recipients achieved normal glucose levels without the need for insulin injections. Ongoing advances in transplantation illustrate how federally funded efforts—among molecular biologists, geneticists, animal researchers, and clinical investigators—lay a solid foundation for improving human health through the effort of a team of investigators.

BIODEFENSE AND TECHNOLOGY RESOURCES

Besides clinical and comparative medicine resources, NCRR also supports biomedical technology centers that develop and provide scientists with access to innovative instruments, technologies, and computational tools. These technology centers have enabled recent advances to help scientists determine how infectious agents, like anthrax, induce their deleterious clinical effects. The anthrax bacterium is unusual because it produces large amounts of a toxin that can kill a patient even after the bacterium itself has been destroyed by antibiotics. A research team used x-ray data collected at an NCRR-supported synchrotron resource to examine the structures of molecules that might disarm the deadly toxin. Synchrotrons are large machines (about the size of a football field) that accelerate electrons to almost the speed of light to produce intense x-rays with adjustable wavelengths that can be exploited to reveal the 3 dimensional structures of molecules. Further structural studies may lead to the development of effective toxin-blocking therapies for inhalational anthrax infections.

In another study, scientists developed improved techniques for identifying microbes by their DNA "fingerprints"—a critical advance in this age of bioterrorism and emerging diseases—and shorten the timeframe needed to identify the toxic agent. Using laser technology at an NCRR-supported flow cytometry resource, scientists analyzed and measured tiny samples of DNA from a Staphylococcus aureus bacterium. The analysis can be completed in just 30 minutes, compared to the 24 hours normally required to analyze DNA. Advanced computational methods linked to the new technology may boost efforts to detect and track microbial threats and provide sufficient time to alert individuals at risk.

INFORMATICS AND INTERDISCIPLINARY SCIENCE

NCRR's shared resources provide a fertile environment for interdisciplinary collaboration. Such studies are essential for addressing important but complex research problems that scientists grapple with today. For instance, NCRR supports a large-scale interdisciplinary effort known as the Biomedical Informatics Research Network (BIRN). That effort draws on multiple resources to examine increasingly complex problems in neuroscience. BIRN is the nation's first test bed for online sharing of research resources and expertise, and for effective data mining for both basic and clinical research. The initial effort focuses on neuroscience, since that discipline holds the largest data sets and requires the capacity to transmit large, information-rich images of the brain. BIRN will be extended to other research areas. Ultimately, the network will enhance the translation of basic research to the patient.

NIH ROADMAP

The NIH Roadmap complements many NCRR programs, and as a result NCRR staff members are involved in virtually every Roadmap Working Group. NCRR is leading the Exploratory Centers for Interdisciplinary Research program. These Centers are developing approaches that will allow researchers from very different scientific disciplines to work together to solve difficult biomedical or behavioral problems. NCRR is also leading the National Technology Centers for Networks and Pathways program that aims to develop new technologies to study molecular interactions within intact cells. NCRR has a significant role in another Roadmap initiative, the National Centers for Biomedical Computing, that will provide the infrastructure needed to promote productive interactions between computational scientists and biomedical researchers.

STRATEGIC PLANNING AND FUTURE INITIATIVES

This past year, NCRR published a new strategic plan for 2004–2008. Titled *Challenges and Critical Choices*, the plan was developed based on input from thousands of researchers and administrators for research-intensive organizations nationwide. This strategic plan now guides NCRR's priorities for programmatic investments. I

would like to briefly describe just a few of the initiatives that NCRR has launched, or plans to launch, to address the plan's recommendations.

Informatics for Clinical Research

The scientists who participated in NCRR's strategic planning process highlighted cyberspace infrastructure that would significantly enhance information sharing, access to and management of vast datasets, and transmission of large data objects like brain images as a priority. NCRR has initiated an assessment to determine current capabilities and future requirements for electronic communication and information management across research centers, including the GCRCs, Research Centers in Minority Institutions, and biomedical technology research centers. One long-term goal is to support collaborations among investigators located in less densely populated states.

Enhance Protection of Clinical Research Subjects

Another important trend identified during NCRR's strategic planning process involves the public's growing concern for the safety of participants in clinical research studies. NCRR created a Research Subject Advocate (RSA) program to assure appropriate safety monitoring of research subjects for GCRC-based studies and to ensure that investigators are aware of their responsibilities under State and Federal law. Because the RSA program has had such a positive impact, NCRR remains committed to strengthening the program.

Expand Availability of Nonhuman Primate Stem Cells

Another NCRR initiative will focus on stem cells, which hold the potential for treating a variety of disorders. But extensive animal studies are needed to identify the molecules, cytokines or other agents that modulate stem cell differentiation. NCRR proposes to support research to identify these factors and to isolate several different embryonic stem cell lines from the rhesus macaque, baboon, and a few other nonhuman primate species. Isolated cell lines will be distributed to qualified scientists via a national resource, and a companion database will track relevant data for each cell line. Information gleaned from these studies may be applicable to the study of human stem cells.

CONCLUSION

In closing, as biomedical research becomes more complex, specialized research resources are required to address emerging trends and build bridges across disciplines. NCRR plays a cross-cutting, trans-NIH role in biomedical research, supporting state-of-the-art resources that enable collaboration and stimulate scientific discovery. These research resources play an essential role in advancing human health.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. DUANE ALEXANDER, DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute of Child Health and Human Development (NICHD). The fiscal year 2006 budget includes $1,277,544,000, an increase of $7,223,000 over the fiscal year 2005 enacted level of $1,270,321, comparable for transfers proposed in the President's request.

With the continued support of this Committee, the National Institutes of Health has the unique ability to invest in complex medical studies that continue for many years. It is particularly satisfying to all of us when an investment in research cures a disease or eradicates a condition. With deep satisfaction, we report a major medical and public health achievement that the *New York Times* heralded a few weeks ago in a front page headline: *U.S. is Close to Eliminating AIDS in Infants.*

This progress came in small incremental steps that arose from a large ambitious vision: to eliminate mother-to-child HIV transmission. Just a decade ago, a pregnant woman with HIV who lived in the United States had more than a 25 percent chance of passing the virus on to her child. In the early 1990s, the NICHD and the NIAID formed the Pediatric AIDS Clinical Trials Group to test promising new anti-HIV treatments. One of the first studies showed that the drug AZT administered to the mother and newborn infant at specific times could reduce HIV transmission from 25 percent to 8 percent. Subsequent research tested a drug combination known as highly active anti-retroviral therapy (HAART) and showed that the rate of transmission could be reduced even further. Today, with an expanded array of anti-HIV

drug treatments, the chance of a pregnant woman in the United States passing the virus on to her child has plummeted to about 1.2 percent.

COMPOUNDS IN MOTHERS' MILK PROTECT AGAINST DIARRHEA

Human breast milk is known to protect infants from diarrhea, but the responsible components had not been known. Results of a routine investigation to understand the purpose of some complex sugar molecules found in human breast milk may lead to a way to prevent diarrheal diseases from occurring, not just in infants, but in older children and adults as well. The molecules, called oligosaccharides, are abundant in human breast milk. During the last decade, NIH-funded researchers have discovered that oligosaccharides can stop bacteria and viruses from binding to the cells in the intestinal wall, preventing diarrheal diseases from gaining a foothold.

Oligosaccharides have been found to combat *E. coli* 0157, the deadly bacterium that can infect ground beef and other common foods. They also block the Norwalk virus, which incapacitates thousands of cruise ship voyagers every year, as well as rotavirus, one of the most common causes of diarrheal diseases in children. Oligosaccharides may also provide a means to overcome the problem of bacterial resistance. They function differently than do antibiotics, and bacteria do not appear able to develop resistance to the oligosaccharides.

RESEARCH LEADS TO BETTER HEALTH FOR WOMEN

Fibroids, or leiomyomas, are painful noncancerous growths that develop in the smooth muscle of the uterus. Women with fibroids may have painful menstrual periods, pain during intercourse, infertility, incontinence, and bowel obstruction. Women with fibroids are also more likely to go into labor prematurely and to experience a miscarriage. The exact number of women with fibroids is not known, but between 25 and 40 percent of all U.S. women experience fibroid symptoms. Fibroids disproportionately affect African Americans. One study estimated that 80 percent of African American women have fibroids by age 60. There are few effective ways other than hysterectomy to treat these tumors. Recently, however, NICHD researchers made some basic discoveries about fibroids that may lead to effective non-surgical treatments. In one study, researchers used sophisticated gene analysis technology to learn that fibroids contained abnormally high levels of a protein known as dermatopontin. That study led to another discovery that fibroids are largely made up of abnormal strands of collagen; thus, researchers are now searching for new drug treatments directed toward the abnormal collagen.

Pregnancy and childbirth place women at higher risk for a disorder known as pelvic organ prolapse, which can be painful and disabling, and require surgical treatment. Although surgical procedures may correct the condition, many women may experience urinary incontinence as a result of such treatment, which may require a second surgery to correct. From early results of a clinical trial, NICHD-funded researchers have learned that performing an incontinence surgical procedure during the same operating room session as the prolapse repair markedly decreases the chances for incontinence, without adverse effects. Such findings not only have implications for improving the quality of life for women, but may have implications for helping to reduce the cost of care.

RESEARCH ENHANCES LEARNING

After more than 30 years of careful research—using the same scientific rigor we use to test a new drug or medical procedure—the NICHD has identified the instructional methods that best help children learn to read. A recent brain imaging study has shown that these scientifically proven methods actually change the brain functioning of formerly poor readers so that it resembles the brain functioning of good readers.

Unfortunately, however, many school districts still rely on instructional practices that are not based on scientific research. According to the National Center for Education Statistics, roughly 37 percent of the nation's 4th graders read below grade level. In collaboration with the Department of Education, NICHD staff is working to communicate evidence-based research findings to provide school districts around the country with new approaches to teach reading. To be competitive in the years ahead, U.S. students will also need a thorough grounding in science. A recent study has challenged current thinking on the best way to teach science. The traditional belief was that students would better remember what they learn if they discovered on their own how to conduct an experiment rather than having someone teach it to them. In fact, the researchers found just the opposite: that students learned faster and retained more information if they were given explicit instructions about ex-

perimental procedures. The finding provides teachers with important information on how best to convey scientific concepts to their students.

Our basic science laboratories continue to produce discoveries of potential clinical relevance to learning and mental retardation. NICHD scientists discovered that a single protein appears central to the formation of the long-term memories underlying all advanced learning. Two teams of NICHD scientists have discovered how the protein known by the acronym BDNF is produced in the brain and are studying whether defects in the BDNF protein system may lead to disorders of learning and memory. Other scientists have studied an animal model of the defective Rett syndrome gene that causes deterioration of cognitive and motor function in girls to learn how the gene causes anatomic and functional abnormalities. Studies also continue on the genetic and neurobiologic bases of autism.

KIDS MAY SAY OTHERWISE, BUT PARENTS MATTER

Several NICHD studies of child development provide strong evidence that parents can exert a direct and positive influence on the decisions that children and young adults make. For example, researchers had suspected for some time that extensive television viewing at an early age might be associated with decreased attention span in children. However, they had no data from long-term studies to support this observation. So NICHD-funded researchers designed a study to answer an important question: do children who watch increasing amounts of TV at 1 and 3 years of age have increase attention problems at age seven? The researchers analyzed data from an ongoing study involving more than 2,600 children and found that the more television very young children watched, the more likely they were at age seven to have attention problems. These findings do not mean that early television viewing is associated with clinically diagnosed attention-deficit/hyperactivity disorder (ADHD). However, the findings support the idea that parents could reduce the risk for attention problems by limiting children's television viewing in their early years.

NICHD scientists have also developed a research-based tool that parents can use to significantly reduce the risks that young, inexperienced drivers face. Insurance companies have known for some time that motor vehicle crash rates are higher for teenagers than for older drivers and are the highest during the first 1,000 miles and the first 6 months of driving. The researchers developed and tested a program in which the central feature is a contract between the parent and new driver. As part of this contract, the newly licensed driver agrees to limit driving at night, driving with other teens in the car, driving on high-speed roads, and driving in bad weather. NICHD research showed that parents can greatly reduce the risks that new drivers face.

REHABILITATION NETWORKS SEEK TO IMPROVE QUALITY OF LIFE

Serious illness and injury may result in life-long impairment. The Traumatic Brain Injury Clinical Trials Network will evaluate new treatments and rehabilitation techniques for children and adults with brain injury. The Pediatric Critical Care Network will evaluate new treatments for children who have suffered a serious injury or illness. The Network will study the effectiveness of short-term treatment and its relationship to the rehabilitation that patients receive and to the long-term outcomes.

THE BEST PHARMACEUTICALS FOR CHILDREN ACT

The NICHD, as directed by law, in consultation with the FDA and experts in pediatric drug development, has identified and prioritized the most important drugs for further study in children. Currently, children are being recruited to study lorazepam for use as a sedative and anticonvulsant, and nitroprusside for controlling blood pressure of children undergoing surgery. In cooperation with the National Cancer Institute, data pertaining to the drugs vincristine and dactinomycin are being reviewed to provide the first evidence-based look at the efficacy, toxicity, and dosing of these two drugs. The evidence from this review will provide the basis for subsequent studies that will provide specific guidance on the use of these drugs in children. Drugs on the current priority list will form the basis of solicitations in 2006.

THE NATIONAL CHILDREN'S STUDY

NICHD scientists working collaboratively with the NIEHS, the CDC, and the EPA continue to make progress in planning the implementation of the National Children's Study as directed by Congress in the Children's Health Act of 2000. The Study, as currently planned, will involve about 100,000 children and their families,

and can form the basis of child health guidance, interventions, and policy for generations to come. Funds in the fiscal year 2005 budget are being used to establish four Vanguard Centers that will pilot recruitment strategies and the Study protocol. A data coordinating center will be established to provide the statistical analysis and reporting of the Study results. The protocol for this Study has been drafted and 101 sites across the United States have been identified to provide a population-based representative sample. These steps bring us closer to the point at which the full study could be implemented.

NIH ROADMAP

The NIH Roadmap initiative is providing an important guide to help the NICHD achieve its research and programmatic goals. The initiative directed to Re-engineering the Clinical Research Enterprise is currently helping to develop future leaders in clinical research. The NICHD is leading several targeted efforts to enhance the training, development, and support of the clinical research teams of the future.

Mr. Chairman and members of this Committee, I would like to thank you for your continued support of our research to improve the health and well being of women, children and families, as well as for your support in the critical task of developing tomorrow's research leaders. I will be pleased to answer any questions.

PREPARED STATEMENT OF DR. JEREMY M. BERG, DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute of General Medical Sciences (NIGMS). The fiscal year 2006 budget includes $1,955,170,000, an increase of $11,103,000 over the fiscal year 2005 enacted level of $1,944,067,000 comparable for transfers proposed in the President's request.

UNDERSTANDING DISEASE REQUIRES UNDERSTANDING NORMAL FUNCTION

As we go about our daily lives, most of us probably forget about the biological processes that make our bodies work. Our cells are constantly making new components, dividing, moving, and even dying. Complex mechanisms underlie each of these processes and elaborate networks integrate them to promote normal, healthy function. If any of these processes break down, the result can be cancer, diabetes, Alzheimer's, or a host of other diseases.

To improve our understanding of basic biological processes, we need to employ a wide range of approaches. These include conducting basic research, developing new technologies, and training tomorrow's scientists. In essence, this is the core mission of NIGMS. For more than 40 years, the Institute has focused on deepening understanding of critical life processes and the molecular underpinnings of disease. In this way, NIGMS lays the foundation for advances in the diagnosis, treatment, and prevention of many different illnesses.

PARADIGM-SHIFTING IDEAS AND THEIR APPLICATION

NIGMS has an impressive track record of investing in research with big payoffs. One indication of this success comes from the many prestigious awards our grantees receive for their research. In each of the last 8 years, at least one Nobel Prize has been given to an NIGMS grantee. This year continues the trend: The 2004 Nobel Prize in chemistry went to Irwin Rose, Ph.D., a biochemist at the University of California, Irvine, whose work has been supported by the Institute for several decades. He brings the number of NIGMS-supported Nobel laureates to 57.

Rose shared the prize for his studies on how cells control the breakdown of unneeded proteins. The mechanism for this controlled breakdown underlies many processes in health and disease and is now the focus of literally thousands of research studies. The discoveries flowing from this basic research are increasingly being translated into new therapies. For example, Alfred Goldberg, Ph.D., an NIGMS grantee at Harvard Medical School in Boston, initiated research that led to a new drug called Velcade®. This drug is used to treat multiple myeloma, a deadly type of bone marrow cancer. Velcade® works by targeting the proteasome—the molecular machine that breaks down unneeded proteins that Rose and his coworkers discovered. Velcade® is likely to be the first of a number of drugs based on the discovery of this process that is so fundamental to much of cell biology.

The path to new approaches for promoting health and preventing and treating diseases has several key elements. These include creatively exploring a range of biological systems, developing tools for expanding knowledge, finding appropriate ways

to integrate this knowledge into practical applications, and, of course, having a workforce of scientists who have the motivation and the knowledge to drive these advances.

FROM CARNIVOROUS SNAILS TO A NOVEL PAIN TREATMENT

It is tough to make a living as a carnivorous snail. A large family of such creatures, called cone snails, relies on extremely potent venom to paralyze prey almost instantly. Baldomero Olivera, Ph.D., a biologist at the University of Utah in Salt Lake City, has been studying cone snails for more than 25 years with NIGMS support, carefully separating the venom into its components and studying each one.

Remarkably, the venom components are small proteins that target structures within the neuromuscular system with exquisite specificity. Because of the roles of their targets and this great specificity, these proteins are powerful research tools and show great promise as drugs. The first drug to result from this work, Prialt®, was approved by the FDA in December 2004 to treat the chronic, intractable pain often endured by people with cancer, AIDS, or certain neurological disorders. One thousand times more powerful than morphine, this new pain medication is thought to be non-addictive.

Other recently discovered pathways are leading to new drugs as well. The process of RNA interference, first characterized in roundworms by NIGMS grantees, can specifically silence individual targeted genes. Harnessing this process has allowed scientists to precisely control genes, leading to exciting new research tools and promising new ways to treat diseases including HIV, hepatitis, and cardiovascular disease. An RNA interference-based drug to treat the blinding eye disease of macular degeneration is currently in clinical trials.

THE SHAPES OF THINGS TO COME

The human genome is expressed primarily through proteins, the molecules that perform virtually all of the body's activities. Based on their amino acid sequences, proteins fold into complex shapes that determine their functions, including which other molecules they bind to form complex assemblies. Powerful techniques have been developed for determining protein structures in great detail. Thousands of such structures have been determined, providing deep insights into how biological systems function in health and disease and driving the development of new drugs and other therapies. Much of this work has been performed by individual investigators working on individual proteins chosen based on their biological context. A productive laboratory might determine two to four structures per year. This approach continues to be effective, but it is too slow to keep up with the vast number of potential protein targets now accessible through genomic studies.

To complement the contributions of individual investigators, NIGMS launched the Protein Structure Initiative (PSI) in 2000 with the goal of developing technologies and processes to enable researchers to quickly, cheaply, and reliably determine the three-dimensional structures of proteins. After 4 years, the nine PSI pilot centers can produce several structures each week, and the total number of structures solved by the PSI centers has now passed the milestone of 1,000!

With the second phase of the initiative beginning this summer, the PSI will use the tools and methods developed in the pilot phase to continue technology development and to determine more protein structures, including some that were too complex to tackle during the pilot phase. Researchers will use these structures to determine and understand protein function, predict the structures of other proteins, identify targets for drug development, design molecules to fit those targets, and compare proteins from normal and diseased tissues.

An important activity related to the PSI is the structural biology component of the NIH Roadmap for Medical Research, which funded two Centers for Innovation in Membrane Protein Production to aid structural studies of this major class of proteins. Difficulties inherent in studying membrane proteins mean that we know relatively little about them, despite the fact that they represent up to a third of all proteins and are the targets for a large number of therepeutic drugs. NIGMS is actively involved in other Roadmap initiatives, as well, including those in the areas of high-risk research (specifically, the NIH Director's Pioneer Award), bioinformatics and computational biology, molecular libraries and imaging, and interdisciplinary research.

COMPUTERS MODEL COMPLEX SYSTEMS

Today's biomedical research has moved beyond describing the parts of living systems to focusing on the complex, dynamic interactions of those parts. One of the

best ways to approach this formidable challenge is to use computers to model and manipulate the systems.

Among the places this is happening are the five NIGMS Systems Biology Centers. Multidisciplinary teams of researchers at these centers are addressing such fundamental questions as how cells divide, differentiate, and communicate and how different kinds of environmental stress affect cell and tissue function.

At the other end of the spectrum, NIGMS-supported researchers are investigating how human systems contribute to the spread of infectious diseases. The researchers, part of the Institute's Models of Infectious Disease Agent Study (MIDAS) initiative, use computational approaches to simulate disease outbreaks, whether they occur naturally or result from bioterrorism. In much the same way as weather forecasters use computer models to predict the landfall of hurricanes, scientists can use the MIDAS models to make predictions about potential epidemics. These models will assist policymakers, public health workers, and other researchers in understanding and responding to new infectious disease outbreaks.

Responding to the medical community's growing concern that avian influenza could cause the next flu pandemic, the MIDAS network currently is simulating the outbreak of a deadly bird flu strain in a hypothetical human community. The computer models incorporate data on population density and age structure, distribution of schools, locations of hospitals and clinics, travel, and the infectiousness of the virus. The models will predict the effects of different strategies to contain the spread of infection, such as vaccinating specific groups of people or restricting travel. Preliminary results from the avian flu modeling project should be available by mid-2005.

DIVERSITY DRIVES DISCOVERY

To continue making rapid progress in biomedical research and improving human health, we need to ensure that the pool of biomedical scientists reflects the great diversity of our nation. This diversity can spark new research questions and offer different approaches to answering them. NIGMS promotes this diversity in a number of ways.

Through our Division of Minority Opportunities in Research, we offer programs that encourage and prepare underrepresented minority students for research careers. Other programs enhance science curricula and faculty research capabilities at institutions with substantial minority enrollments.

We require our institutional training programs to recruit and retain underrepresented minority students, as well. And we promote diversity of ideas through interdisciplinary training programs and through efforts to bring the expertise of researchers in a variety of fields, from the physical to the behavioral sciences, to bear on biomedical questions. One example is our partnership with the National Science Foundation that supports more than 30 research grants at the interface of biology and mathematics.

EXPANDING THE HORIZON

Our increasing knowledge of the biological processes that underpin health and disease holds great promise for new drugs and better diagnostic techniques in the future. A more complete picture of how these processes work—and don't work—may lead to new methods for preventing illness altogether.

At the same time, it is important to remember that breakthroughs are often based on years of scientific research, with each new result building on many previous ones. Each discovery pushes back the frontier and reveals intriguing new questions and avenues for future study. While we can't always predict what we'll find, we can guarantee that the journey will bring us closer to our goal of understanding human health and disease.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. FRANCIS S. COLLINS, DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Human Genome Research Institute (NHGRI). The fiscal year 2006 budget includes $490,959,000, an increase of $2,351,000 over the fiscal year 2005 enacted level of $488,608,000 comparable for transfers proposed in the President's request.

Cable News Network (CNN) recently named the completion of the Human Genome Project (HGP) the number one health news story of the past 25 years. CNN reported, "Much of the marvel of medicine has to do with discovery. Mapping the human genome, the complete sequence of DNA, gave scientists a blueprint for building a person, making it the No. 1 medical story, according to a distinguished panel CNN gathered to rank the top 25 medical stories of the past quarter-century." As the leader of the HGP, the National Human Genome Research Institute (NHGRI) is very proud of this recognition, but as CNN also pointed out there is still a great deal more to learn.

ONGOING NHGRI INITIATIVES

Analysis of the Completed Human Genome Sequence

In October 2004, the International Human Genome Sequencing Consortium, led in the United States by the NHGRI and the Department of Energy, published a description of the finished human genome sequence in the journal Nature. An international team worked to convert the draft genome, published in 2001, into a highly accurate form. The new analysis reduces the estimate of the number of human protein-coding genes from 35,000 to only 20,000–25,000—a surprisingly low number for our species, considering that only a decade ago most scientists thought there would be over 100,000 genes. We now focus on the more difficult task of understanding the function of each of these genes.

Use of Comparative Genomics to Understand the Human Genome

The availability of the genome sequences of the human, the mouse, the rat and a wide variety of other organisms is driving the development of an exciting new field of biological research, comparative genomics. The NHGRI is funding research comparing the finished reference human genome sequence with that of other organisms, to identify regions of similarity and difference, thus dramatically increasing understanding of the structure and function of human genes to enable development of new strategies to combat human disease.

ENCyclopedia Of DNA Elements (ENCODE) project

With the goal of identifying the precise location and function of all sequence-based functional elements in the human genome, the NHGRI launched the ENCyclopedia Of DNA Elements (ENCODE) project in the fall of 2003. The project is an international consortium of computational and laboratory-based scientists open to all investigators who agree to abide by the project's criteria and guidelines for participation. A manuscript describing the ENCODE project appeared in the October 22, 2004 issue of Science, detailing the rationale and strategy behind the quest to produce a comprehensive catalog of all parts of the human genome crucial to biological function, including all protein-coding genes, non-protein-coding genes, regulatory elements involved in the control of gene transcription, and DNA sequences that mediate chromosomal structure and dynamics. All data generated for the ENCODE project are being deposited in free, public databases as soon as they are experimentally verified.

Progress with the HapMap

All diseases have a hereditary component, but for most common diseases like diabetes, heart disease, and mental illness, the gene variants responsible for the increased risk have been difficult to identify. To solve this problem, an approach to scan large regions of chromosomes to find the genetic variants (called SNPs, or single nucleotide polymorphisms) that increase or decrease the risk of disease is needed. NHGRI has taken a leadership role in the International HapMap Consortium and the development of the HapMap (haplotype map), a catalog of human genetic variations and how that is organized into haplotype "neighborhoods" across the gene. Researchers are already starting to use the HapMap to find genes and variants that contribute to many diseases; it will also be a powerful resource for studying the genetic factors contributing to variation in individual response to disease, drugs, and vaccines.

In February 2005, the International HapMap Consortium completed phase I of the project, ahead of schedule. Boosted by an additional $3.3 million in public-private support, the NHGRI announced plans to create an even more powerful map of human genetic variation than originally envisioned. The consortium's new goal is an improved version of the HapMap about five times denser than the original plan. This "Phase II" HapMap will test another 4.6 million SNPs from publicly available databases and add that information to the map. The HapMap will be completed in the fall of 2005.

Gene Variants May Increase Susceptibility to Type 2 Diabetes

Understanding the genetic basis of the more common, polygenic diseases has traditionally been very difficult. But the tools of genomics, especially HapMap, are beginning to reveal many details about the risk of common diseases that had previously been unapproachable. One disease for which excellent progress has been made towards understanding its genetic cause is Type 2 diabetes. Affecting about 17 million people nationwide, it accounts for 90 to 95 percent of all diabetes cases in the United States. This past year, two international research teams, including one at NHGRI, each found variants in a gene that appears to predispose people to type 2 diabetes, the most common form of the disease. Homing in on a wide stretch of chromosome 20, the teams identified four genetic variants (SNPs) that are strongly associated with type 2 diabetes in Finnish and Ashkenazi Jewish populations and that appear to raise the risk of type 2 diabetes by about 20 to 30 percent. Translating this discovery into a treatment that benefits people with diabetes or those at risk is still years away, but this is a major step in that direction.

NEW INITIATIVES

Roadmap—Chemical Genomics

The Molecular Libraries Roadmap initiative will offer public sector researchers access to libraries of novel small organic molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways. This marriage of chemistry and biology will provide new ways to explore the functions of major components of cells in health and disease. In June 2004, NHGRI announced the establishment of the NIH Chemical Genomics Center, and up to eight pilot extramural centers will be funded at academic institutions and other locations across the country in the spring of 2005. These will function as an integrated network, including a common publicly available database (PubChem, already activated in September 2004) which will display the results of all screens of chemical compounds.

Human Cancer Genome Project

The dramatic drop in costs of DNA sequencing, catalyzed by the Human Genome Project, now makes it possible to use sequencing as a major tool for medical research. Doctors and research scientists have long known that cancer is, essentially, a genetic disease. Inherited mutations or acquired genetic alterations can set a normal cell on a path of uncontrolled growth and malignancy. It is now conceivable to identify the complete universe of genes involved in every type of cancer. That is the intent of a bold new NCI/NHGRI proposal for a Human Cancer Genome Project. Such a complete inventory of cancer genes will provide powerful new ways to prevent, diagnose, and treat every major form of the disease.

The $1,000 Genome Project

The ability to determine the complete genome sequence of an individual could revolutionize medical care. In October 2004, NHGRI awarded more than $38 million in grants to spur the development of innovative technologies designed to reduce the cost of DNA sequencing dramatically. NHGRI's near-term goal is to lower the cost of sequencing a mammalian-sized genome to $100,000, which would enable researchers to sequence the genomes of hundreds or even thousands of people as part of studies to identify genes that contribute to cancer, diabetes, and other common diseases. Ultimately, NHGRI's vision is to cut the cost of whole-genome sequencing to $1,000 or less, which would enable the sequencing of individual genomes as part of medical care. The ability to sequence each person's genome cost-effectively could give rise to more individualized strategies for diagnosing, treating, and preventing disease. Such information could enable doctors to tailor therapies to each person's unique genetic profile.

The U.S. Surgeon General's Family History Initiative

The U.S. Surgeon General's Family History Initiative was launched on November 8, 2004, with the NHGRI as the lead collaborating federal agency. The purpose of this national public health campaign is to: increase the awareness of the American public and their health professionals about the importance of family history in health; provide tools to gather, understand, evaluate, and use family history to improve health; give health professionals tools to communicate with patients about family history; and increase genomic and health literacy. A web based and print tool entitled "My Family Health Portrait" was developed in both English and Spanish to facilitate collection of family history data. To date, the initiative has been highlighted in more than 1,000 media stories and over 170,000 copies of the tool have been distributed via the World Wide Web and in paper form. This public health campaign is intended to be an annual event.

ELSI Centers for Excellence Program

On August 31, 2004, the NHGRI's Ethical Legal and Social Implications (ELSI) research program announced the funding, with contributions from the Department of Energy and the National Institute of Child Health and Human Development, of four interdisciplinary centers as part of its Centers for Excellence in ELSI Research (CEER) program, a new initiative to address some of the most pressing ethical, legal, and social questions facing individuals, families, and communities in the genome era. Each of the centers, based at Duke University, Case Western Reserve University, Stanford University, and the University of Washington, will assemble a team of experts in several disciplines, such as bioethics, law, behavioral and social sciences, clinical research, theology, public policy, and genomic research.

OTHER AREAS OF INTEREST

Genetic Education for Health Care Professionals

The NHGRI has developed numerous educational programs to prepare health care professionals for the integration of genomics into primary health care. A new effort by the NHGRI in this area in 2004 was its work with the American Academy of Family Physicians (AAFP) to develop the AAFP's 2005 Annual Clinical Focus program, which has Genomic Medicine as its theme.

Genetic Nondiscrimination

Possibly the greatest impediment to the advancement of genomic science and its application to human health is the fear of genetic discrimination. The NHGRI has worked for ten years to realize a federal solution to this problem. The Secretary's Advisory Committee on Genetics Health and Society has also strongly supported the need for federal legislation. On February 17, 2005 the Senate passed the Genetic Information Nondiscrimination Act of 2005 (S. 306), which would address these fears, and the Bill has now been referred to the House. The Bush Administration has also issued a Statement of Administrative Policy in support of the legislation. This issue remains a high priority for the Institute.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee might have.

PREPARED STATEMENT OF DR. PATRICIA A. GRADY, DIRECTOR, NATIONAL INSTITUTE OF NURSING RESEARCH

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute of Nursing Research (NINR). The fiscal year 2006 budget includes $138,729,000, an increase of $657,000 over the fiscal year 2005 enacted level of $138,072,000 comparable for transfers proposed in the President's request.

I appreciate the opportunity to appear before you today to discuss the exciting work of the National Institute of Nursing Research (NINR) that provides important science to provide necessary improvements in the quality of patient care across the continuum of life. Unique within the NIH, our mission is structured around the science that connects health care providers to patients, their families, and caregivers.

There are many components to our society's healthcare mosaic. Care is delivered through a variety of settings: conventional healthcare sites, community-based clinics, and homes. Patients with exceptional needs—from newborns, the disabled, individuals at the end-of-life—and the underserved, from urban to rural settings, rely on quality care. Through our studies, we seek to understand and manage the symptoms of acute and chronic illness, and thus, to find effective approaches to achieving and sustaining good health.

Let me now share with you some examples of how our research is changing patient care and improving lives.

MOTHERS AND THEIR YOUNG CHILDREN WITH ASTHMA

Asthma, a chronic and sometimes life threatening condition, is associated with high health costs related to medications, outpatient management, and emergency room visits. Especially for younger children, good asthma management requires close vigilance by the parent or caregiver. Researchers in one study interviewed working mothers of young, inner-city asthmatic children, more than a quarter of whom reported that there was a smoker in the house. While most of the children were under the care of a doctor and were prescribed appropriate asthma medications, many still experienced frequent coughing, wheezing, or shortness of breath.

The mothers often did not give medications for coughing, which can be an early sign of an asthma attack. While most were vigilant and strove to provide good asthma management, the study demonstrated that many mothers lack sufficient information on early asthma symptoms and need additional education about asthma in order to provide the best care for their children.

HEALTH DISPARITIES IN RURAL COMMUNITIES

The health care of rural populations is a concern because of poverty, lack of services and/or health vulnerability of the population. NINR's recently funded Rural Nursing and Health Care Research Center provides an interdisciplinary research infrastructure to conduct and disseminate nursing research to address the needs of rural populations. NINR has funded researchers who are making advances with technological interventions for the chronically ill rural populations. The Women to Women project is a computer-based communication intervention that is testing a program of health information and social support for women. The program provides educational tools for self-management skills and studies the risks of isolation and chronic illness. This project has influenced health outcomes by creating a more informed and self-managing patient population. The program may ultimately serve as a model to deliver support and education to remote or vulnerable populations.

CARING FOR THE CAREGIVERS

Dementia-related conditions cause a progressive decline in memory, cognition, and physical function, and affect nearly 10 percent of persons over 65 years of age. The behavior of the patient with dementia can range from forgetfulness to dangerous and aggressive activities. Family caregivers often identify the management of this behavior as a major source of distress and burden.

The Savvy Caregiver Program, an educational program for caregivers, increased the skill, knowledge, and confidence of caregivers. In addition, most caregivers reported a decreased sense of burden and improved ability to deal with dementia-related behavior of the patient. The caregivers underscored their belief in the benefits of caregiving, and stated they would recommend the program to others.

When family caregivers cannot manage the patient with dementia at home, they often must place the person in a long term care facility. The Family Involvement in Care program was developed to help family members contribute to the care of the institutionalized patient. This project tested a program for the nurses and staff on the impact of dementia for the family, and on ways to support a continued family presence. Family members reported more positive feedback to the facility, while the staff participants reported positive outcomes regarding the family caregiving role.

RESEARCH ON CARE AT THE END OF LIFE

The end-of-life process includes numerous challenges: physical, emotional, spiritual, and financial. There also are challenges in health care systems exacerbated by the lack of continuity among caregivers, disruption of social support networks, unshared clinical information, and multiple physical locations for care. Family members experience role changes, stress, and ultimately, bereavement as their loved one traverses life's continuum.

The NINR is charged with leading the Institutes and Centers for advancing a trans-NIH research agenda on end-of-life care. In this role, we support a broad range of studies designed to improve the management of symptoms associated with the end of life; elucidate the broad issues that affect many families across the nation such as communication among patient, family, and care providers; enhance coping with terminal illness; and examine cultural and ethnic influences on end-of-life care.

In one NINR study, researchers interviewed patients with terminal cancer and found that spiritual well-being helped reduce depression, hopelessness, thoughts of suicide, and the desire to hasten death. The investigators concluded that palliative care clinicians should assess the spiritual beliefs and needs of their terminal patients to help them cope with despair and achieve a sense of peace and meaning in their life.

In December 2004, NINR cosponsored an NIH state-of-the-science conference on end-of-life. Nearly one thousand people from around the world came to NIH to review the existing knowledge base on end-of-life and to recommend opportunities for future research. These recommendations will feature prominently in NINR's forthcoming research plans in this area.

PALLIATIVE AND END-OF-LIFE CARE IN RURAL AND FRONTIER AREAS

Residents living in rural or frontier areas typically have limited access to health care services, particularly at end-of-life. In fiscal year 2006, NINR will initiate studies focused on understanding the scope of the problems associated with limited access to care in rural areas. These studies will examine ways to improve end-of-life care through the use of technology; develop new methods to use existing networks and services; design culturally appropriate interventions for palliative care; and identify possible alternative settings and methods for providing care and supporting family caregivers.

BUILDING NURSING RESEARCH CAPACITY

As our nation is experiencing a shortage of nurses, we are also experiencing a shortfall in the number of nurse scientists. NINR is building research capacity with several innovative initiatives, collaborating with universities nationwide to rapidly develop baccalaureate-to-doctoral fast-track programs. The Graduate Partnership Program (GPP) in Biobehavioral Research, a new pilot training program, partners schools of nursing with the NIH intramural program to provide cutting-edge, mentored research training for outstanding doctoral students.

NINR is also supporting Centers to stimulate research and research training opportunities. One example, the *Nursing Partnership Centers to Reduce Health Disparities,* together with the National Center on Minority Health and Health Disparities, partners research-intensive universities with minority-serving institutions.

NINR AND THE NIH ROADMAP

NINR has identified two key areas of science within the NIH Roadmap, Interdisciplinary Research Teams of the Future and Re-engineering the Clinical Research Enterprise, and integrated them within the nursing research agenda. NINR and its investigators have extensive experience in conducting interdisciplinary research projects. Currently, more than one-half of NINR-funded studies appear in non-nursing journals. This shows the promise of future interdisciplinary collaborations and the value of nursing research findings by other disciplines. In the area of improving the clinical research enterprise, most of NINR's research is clinical in nature and research questions are evaluated from the clinical researcher's perspective. Investigators translate research findings into the clinical practice of healthcare providers and develop partnerships to speed new scientific knowledge into mainstream health care.

CONCLUSION

In conclusion, NINR strives to improve the quality of life and quality of health through every stage of life, especially for the most vulnerable in our society. We are committed to training the next generation of nurse researchers, and to continuing to fund rigorous and innovative programs of research to enhance the health of our nation.

Thank you, Mr. Chairman. I will be pleased to answer any questions that the Committee might have.

PREPARED STATEMENT OF DR. RICHARD J. HODES, DIRECTOR, NATIONAL INSTITUTE ON AGING

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute on Aging (NIA). The fiscal year 2006 budget includes $1,057,203,000, an increase of $5,213,000, or 0.5 percent over fiscal year 2005 enacted level of $1,051,990,000 comparable for transfers proposed in the President's request.

Thank you for the opportunity to participate in today's hearing. I am Dr. Richard Hodes, Director of the National Institute on Aging, and I am pleased to be here today to tell you about our progress making and communicating scientific discoveries that will improve the health and well-being of older Americans.

There are today approximately 35 million Americans ages 65 and over, according to the U.S. Bureau of the Census, and this number is expected to rise dramatically in the coming decades. The mission of the National Institute on Aging (NIA) is to improve the health and well-being of these older Americans through research. In support of its mission, the Institute conducts and supports an extensive program of research on all aspects of aging, from the basic cellular and molecular changes that occur as we age, to the prevention and treatment of common age-related conditions,

to the behavioral and social aspects of growing older, including the demographic and economic implications of an aging society. In addition, the NIA is the lead federal agency for research related to the all-important effort to prevent and treat Alzheimer's disease (AD). Finally, our education and outreach programs provide vital information to older people across the Nation on a wide variety of topics, including living with chronic conditions, maintaining optimal health, and caregiving.

ALZHEIMER'S DISEASE AND THE NEUROSCIENCE OF AGING

AD is a devastating condition with a profound impact on individuals, families, the health care system, and society as a whole. Approximately 4.5 million Americans are currently battling AD, with annual costs for the disease estimated to exceed $100 billion.[1] Moreover, the rapid aging of the American population threatens to increase this burden significantly in the coming decades: By the year 2050, the number of Americans with AD could rise to some 13.2 million, an almost three-fold increase.[2]

These statistics lend an urgency to the NIA's efforts to better understand, prevent, and treat AD, and in the past year, we have made several important steps forward. For example, a priority for the NIA is to identify risk factors for AD, as interventions that impact the effect of a risk or preventative factor could potentially delay the onset of the disease or prevent it altogether. Results from several recent studies have associated diabetes, which affects about one in five persons over age 60 years,[3] with increased risk of cognitive impairment, including AD, raising the possibility that prevention strategies for diabetes may also have major consequences for preventing or delaying AD.

Evidence is also mounting that lifestyle choices may affect risk of AD. In one recent study, older dogs on a regimen of regular physical exercise and mental stimulation and a diet fortified with plenty of fruits, vegetables, and vitamins performed better on cognitive tests and were better able to learn new tasks than dogs in a "control group." Although the results of this study need to be replicated in humans, they do provide evidence that diet and mental exercise may protect against late-life cognitive decline, and that they may work more effectively in combination than by themselves.

An area of some controversy has been the effects of hormonal influences on cognitive aging in women, with some studies demonstrating a decreased risk for AD among users of hormone therapy and others, notably the Women's Health Initiative Memory Study (WHIMS), showing that post-menopausal women on certain regimens were actually at higher risk for cognitive decline. The risks and benefits of hormone therapy remain under study. One new avenue of inquiry is the use of selective estrogen receptor modulators (SERMs) to prevent cognitive decline. SERMs mimic estrogen's actions in some tissues but block the action of the body's naturally occurring estrogen in others, offering the benefits of traditional hormone therapy with fewer potential health risks. In a recent study, the SERM raloxifene (Evista®), frequently prescribed for the prevention and treatment of osteoporosis, appeared to reduce the risk of cognitive impairment in postmenopausal women. More research is needed, but this is a promising area of research.

The first NIH AD prevention trial, comparing the effects of vitamin E and donepezil (Aricept®) in preventing AD in people diagnosed with mild cognitive impairment (MCI), often a precursor condition to AD, recently concluded. Preliminary data indicate that people with MCI taking donepezil were at reduced risk of progressing to AD for the first 18 months of the 3-year study when compared with their counterparts on placebo. The reduced risk of progressing from MCI to a diagnosis of AD disappeared after 18 months, and by the end of the study, the probability of progressing to AD was the same in the two groups.

NIA is currently supporting over 20 additional AD clinical trials, including large-scale prevention trials, which are testing agents such as anti-inflammatory drugs, statins, homocysteine-lowering vitamins, and anti-oxidants for their effects on slowing progress of the disease, delaying AD's onset, or preventing the disease altogether. Trials are also assessing interventions for the behavioral symptoms (agita-

[1] Data from the Alzheimer's Association. See also Ernst, RL; Hay, JW. "The U.S. Economic and Social Costs of Alzheimer's Disease Revisited." American Journal of Public Health 1994; 84(8): 1261–1264. This study cites figures based on 1991 data, which were updated in the journal's press release to 1994 figures.

[2] Hebert, LE et al. "Alzheimer Disease in the U.S. Population: Prevalence Estimates Using the 2000 Census." Archives of Neurology August 2003; 60 (8): 1119–1122.

[3] See http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm. Statistics are taken from the 1999–2001 National Health Interview Survey and 1999–2000 National Health and Nutrition Examination Survey (estimates projected to year 2002).

tion, aggression, and sleep disorders) of people with AD. The Institute also supports the development of new agents for AD prevention and treatment, including chemical compounds to validate new drug targets, an activity with relevance to the "Molecular Libraries" area of the NIH Roadmap.

This year, we have moved forward with two major AD initiatives. The Alzheimer's Disease Neuroimaging Initiative, a longitudinal, prospective, natural history study of normal aging, mild cognitive impairment, and early AD to evaluate neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET), was funded, with funding also identified for several ancillary studies. This ambitious initiative is being implemented jointly with several other NIH Institutes, academic institutions, and industry partners, and exemplifies the potential for scientific discovery that is the goal of the NIH Roadmap component on Public-Private Partnerships.

The NIA is accelerating the pace of Alzheimer(s disease genetics research with its AD Genetics Initiative, a major new program to speed the creation of a large repository of DNA and cell lines from families with multiple AD cases. The goal of this initiative is to develop the resources necessary for identifying the remaining late-onset AD (LOAD) risk factor genes, associated environmental factors, and the interactions of genes and the environment. To aid recruiting efforts, the NIA Alzheimer's Disease Education and Referral Center worked closely with the Alzheimer's Association as well as several academic partners to publicize the initiative.

In addition to AD, the NIA supports research on other neurological diseases, including Parkinson's disease, frontotemporal dementia, and prion diseases. For example, NIA investigators, along with researchers from the National Institute of Neurological Disorders and Stroke, were part of an international research team that identified a mutation that is believed to be the most common genetic cause of Parkinson's disease identified to date. This discovery could lead to the development of a test to detect the mutation in individuals at risk.

OTHER AGING-RELATED RESEARCH

Diseases of aging continue to affect many older men and women, seriously compromising their quality of life. Diseases and conditions currently under study at the NIA include:

Anemia.—Recently, NIA investigators found an overall prevalence of anemia of 11 percent in men and 10.2 percent in women ages 65 years and older, with prevalence increasing dramatically over age 85. The American Society of Hematology (ASH) has worked closely with several NIH institutes to establish a research agenda on anemia in the elderly. An ASH workshop, "Clinical Implications of Anemia in the Elderly," was held in March 2004 to establish a research agenda on anemia in the elderly; a report of this workshop will be published in the journal Blood in spring 2005. Program staff from NIA and several other NIH Institutes participated in the ASH workshop and will work collaboratively to identify research priorities. In addition, the NIA is developing an initiative to stimulate a broad range of research on anemia in the elderly that will inform efforts to decrease the associated functional impairment, morbidity and decreased survival.

Obesity.—According to the National Health and Nutrition Examination Survey, some 64 percent of U.S. adults are either overweight or obese. Excess weight and obesity are linked with an array of conditions, including diabetes, osteoarthritis, and cardiovascular disease. As we age, we tend to gain fat, which may interfere with the work of tissues in which it accumulates. For example, marrow in most bones becomes partially or wholly replaced by adipose (fat) cells, and fat accumulates around and infiltrates the bundles of muscle fibers in muscles of the limbs and trunk. The accumulation of fat in the muscle appears to be doubly dangerous, interfering with both mechanical function of the muscles and insulin sensitivity. The NIA is planning an initiative to stimulate research exploring adipogenesis in aging—i.e., the origin of the increased propensity to form fat cells, and its impact on tissues and systems. This area of research has the potential to broadly impact our understanding of both the decline in function of individual tissues in the musculoskeletal system, and the frequently seen changes in glucose metabolism and insulin sensitivity with age.

Elder Abuse and Mistreatment.—Many older Americans are vulnerable to mistreatment, including physical and psychological abuse, neglect, and financial exploitation. However, the scope of the problem remains unknown. The National Research Council (NRC), at the request of the NIA, established a Panel to review risk and prevalence of elder abuse and neglect. The Panel's 2003 report, *Elder Mistreatment. Abuse, Neglect, and Exploitation in an Aging America*, outlines a number of key priorities, including the development of operational definitions of elder mistreatment

and the development of reliable and valid measures of prevalence. To that end, the NIA is planning a pilot program to develop the tools to accurately assess the prevalence of elder abuse, a necessary first step in developing interventions.

A number of the NIH Roadmap initiatives are particularly relevant to aging research. For example, small molecule development, by providing chemical compounds to validate new drug targets, is crucial to the development of drugs for a variety of age-related diseases, degenerative conditions, and disabilities. Another Roadmap initiative has established a network of investigators to improve the measurement of patient-reported outcomes, and ongoing projects of particular relevance to the aged population are addressing pain, fatigue, arthritis, psychiatric symptoms, including depression, and social functioning.

HEALTH COMMUNICATIONS AND PROMOTION

Last year, the NIH launched NIHSeniorHealth.gov, a unique web site developed by NIA and the National Library of Medicine and geared toward the health needs of older adults. In its first year, the site was extremely successful, attracting some 380,000 unique visitors and garnering over three million page views. It was the only web site to receive an "Industry Innovators Award" from the International Council on Active Aging. A Spanish-language version of the site is currently under development.

Meals on Wheels Initiative.—During a 2002 Congressional hearing, it was recommended that NIA and the Administration on Aging (AoA) work together to disseminate research-based consumer education materials to the thousands of seniors who participate in the Meals-on-Wheels (MOW) program. In participation with AoA, NIA conducted focus groups with the MOW Association of America to identify the types of information of greatest interest to MOW's clients and the best ways to deliver such information. Now, a new booklet entitled "Take Your Medicines the Right Way—Everyday!"is being made available to MOW providers for their clients free of charge. The booklet is in easy-to-read language and covers important steps to help ensure safe and effective medication use.

DEMOGRAPHY

As the percentage of Americans over age 65 increases, profound societal changes will likely occur. NIA-supported researchers are exploring the changing demographic, social, and economic characteristics of the older population. The results of this research often have important implications for public policy. A major source of demographic data on aging is the Health and Retirement Study, a biennial survey of more than 22,000 Americans over age 50, which provides data for researchers, policy analysts, and program planners who are making major policy decisions that affect retirement, health insurance, saving and economic well-being. In 2004, the NIA added a cohort of "Early Baby Boomers" to this study; this will provide crucial information on the savings, retirement, and health behaviors of tens of millions of Americans now approaching retirement age.

Thank you for the opportunity to testify before this Subcommittee. I would be happy to answer any questions you may have.

PREPARED STATEMENT OF DR. SHARON H. HRYNKOW, ACTING DIRECTOR, FOGARTY INTERNATIONAL CENTER

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's Budget for the Fogarty International Center (FIC). The fiscal year 2006 budget includes $67,048,000, which reflects an increase of $416,000 over the fiscal year 2005 enacted level of $66,632,000 comparable for transfers proposed in the President's request.

Many years ago, President John F. Kennedy noted that "A rising tide lifts all the boats. And a partnership, by definition, serves both partners, without domination or unfair advantage." These words serve to remind us of the importance of working in partnership with those around the world, on equal footing, and for the common good. Congressman John E. Fogarty, for whom our Center is named, also shared this belief and worked tirelessly to champion improved health of Americans in a healthier world—through international health research and training programs.

Today, the vision of Congressman Fogarty continues to inspire the Center in building international partnerships on behalf of the National Institutes of Health (NIH) and in supporting research and training programs to advance the objectives of global health. FIC's unique mission and initiatives add value, complement NIH

international programs and build scientific capacity around the world for the benefit of Americans and the global community.

I welcome this opportunity to discuss briefly FIC's progress over the past year as well as our proposed plans for fiscal year 2006. Developed with the support and guidance of the Administration and this Committee, the Fogarty programs reflect our nation's enduring commitment to global health as well as vibrant, and equal, international collaborations.

GLOBAL BURDENS OF ILL HEALTH

The health challenges we face as Americans and as members of a global community are many. HIV/AIDS and tuberculosis continue to rise at alarming rates. SARS, West Nile Virus, and avian flu are constant threats to global health and economies. At the same time, as chronic diseases such as cancer, cardiovascular disease, and mental health disorders increase year after year, taking enormous tolls in human suffering and economic costs, the development and deployment of more effective preventive and treatment measures is urgent.

The Fogarty response to these challenges is to support a range of critical research and training programs, each designed to tackle specific health problems shared by United States and foreign populations. We work in partnership with universities in the United States, low- and middle-income nations, and our fellow Institutes at the NIH, the Centers for Disease Control and Prevention, the World Health Organization, and others to effect change. Fogarty supports over 20 research and training programs in more than 100 countries, involving more than 5,000 scientists in the United States and abroad. HIV/AIDS, TB, maternal and child health, environmental health and bioethics are just a few of the priority program areas in which Fogarty and its partners are making an impact.

IMPACT OF FOGARTY PROGRAMS

I want to share with you two examples to highlight the impact of Fogarty programs worldwide. The first is a genealogy of sorts of one scientist's career path and support by Fogarty. Dr. Lee Riley of the University of California at Berkeley traces his professional roots to Dr. Warren D. Johnson, Jr. of the Weill Medical College of Cornell University. Both have dedicated decades of their professional careers to understanding, preventing, and treating infectious diseases in the slums of Brazil. It all started in 1988 when Dr. Johnson received FIC support to train AIDS scientists in Brazil. When Dr. Riley joined the Cornell faculty in 1990, Dr. Johnson brought him into the AIDS training effort and allowed Dr. Riley to initiate additional training activities on tuberculosis diagnostics and pathogenesis. When Dr. Riley moved to the University of California at Berkeley in 1996, he competed successfully for his own training program in Brazil through Fogarty's International Training and Research in Emerging Infectious Diseases Program (ITREID). Dr. Johnson received a similar ITREID program grant at Cornell, enabling the two to coordinate and synergize their training activities. Dr. Riley's group ultimately expanded the ITREID program to other countries in Latin America as well as to Eastern Europe, and Dr. Riley competed successfully for a new FIC-supported grant on Global Infectious Disease Training and Research in Brazil.

The results and impact of these 17 yearlong partnerships have been enormous. In terms of people and publications, thirty Brazilian investigators have been trained in the United States, 29 of whom are still active researchers in Brazil; 28 articles have been published in top scientific journals; 12 Ph.D. and 3 Masters degrees in public health have been conferred; and, a large number of allied health professionals, many of whom are or were residents of slums, have received project-related training. Just one of the trainees who has returned to Brazil, Dr. Albert Ko, has trained over 50 local staff—both laboratory and field—over the last eight years, and he has now received his own FIC training award. Other trainees are applying for and are receiving funds from NIH and other research agencies.

Critically, the wealth of knowledge generated has been enormous. New understandings have emerged of the causes and treatments of leptospirosis, a disease that impacts primarily young people. Patterns of the spread of tuberculosis in crowded situations have been uncovered, and prevention strategies deployed. Training of health scientists from Brazil through the FIC AIDS training programs led to a major research grant from the National Institute of Allergy and Infectious Diseases for the study of the pathogenesis of leishmaniasis in Brazil and for a subsequent Fogarty award in infectious disease training. Training through the FIC AIDS training programs has helped Brazil evaluate the effectiveness of antiretroviral therapy programs that have served as a model and inspiration to other developing countries. The partnerships have generated millions of dollars of additional support from

Brazil, Spain, Mexico, and other nations to sustain the research and training activities. And, the relationships and partnerships that have been built over time are the ones that will allow future studies to move ahead expeditiously.

The second example is from a research project involving a 1996 pilot program in Orizaba, Mexico working to evaluate the impact of Directly Observed Therapy (Short-Course) (DOTS) in populations with drug-resistant tuberculosis. DOTS is the WHO recommended TB treatment regimen whereby TB patients are monitored daily to ensure that medications are taken properly. In this region, 21 percent of the new cases were resistant to at least one anti-tuberculosis drug and 3 percent were multi-drug resistant (MDR) over a five-year period. The data collected demonstrated that DOTS could rapidly reduce transmission and the incidence of both drug-susceptible and drug-resistant tuberculosis. The case rates of multi-drug resistant tuberculosis were also reduced; however, the fatality rate was highest (12 percent) for patients infected with resistant strains. In a developing country with a moderate rate of drug-resistant tuberculosis, DOTS can rapidly reduce the transmission of both susceptible and resistant organisms. Additional studies are now under way to expand on these initial findings.

FISCAL YEAR 2006 INITIATIVES

FIC will continue to support the NIH Roadmap for Medical Research in the 21st Century. Working with partners across NIH and universities around the world, FIC will foster interdisciplinary programs in clinical research training, identify novel technologies to combat global health threats, and expand efforts to bring experts from multiple disciplines together to advance NIH Roadmap goals. In keeping with the Roadmap, FIC will work in fiscal year 2006 to bring new partners into the global health enterprise. FIC will support the Framework Programs for Global Health to link multiple schools within the same university (or coupled universities) around the topic of global health, bringing business, journalism, social science, engineering, medicine, law, public health and other disciplines into the global health arena in the university setting. A second goal will be to energize the next generation of global health leaders through development of undergraduate and graduate curricula on global health. This effort will propel global health efforts forward in new ways in the United States and abroad.

FIC will enhance its two main programs to address HIV/AIDS and related TB challenges. Fogarty's AIDS International Research and Training Program builds capacity in resource poor nations to tackle the AIDS problem through science and evidence-based policies. Working through 25 U.S. universities, educational programs support post-doctoral, doctoral, Masters level work, and training for allied health professionals, including nurses, to advance research on vaccine development and microbicide development, to identify groups at high-risk for exposure and to help support the development of interventions that make sense at the local and community levels. Nearly 2,000 developing country researchers from over 100 countries have been trained in the United States, many at senior levels, and more than 50,000 through in-country workshops and courses. More than 80 percent of those trained in the United States through this program returned home to pursue research and health efforts locally. And, recognizing the need for clinical and health systems researchers for AIDS and TB, FIC launched a unique International Clinical, Operational and Health Services Research Training Award program to meet these needs. Today, under this program, experts in Uganda, Haiti, Russia, and China are working with U.S. partners to advance AIDS prevention and treatment strategies through targeted training efforts and to monitor the effectiveness of AIDS drug delivery paradigms. These programs support the goals of the President's Emergency Plan for AIDS Relief and the Global Fund and will lead to useful insights about effective drug delivery approaches in resource poor nations.

As a third emphasis area, FIC will expand in fiscal year 2006 its pilot program to support NIH Alumni Associations abroad. These Associations will serve an important role to junior scientists as they return home through support of networking activities in which to share information and expertise, and other activities. At the same time, they will allow U.S. scientists to maintain collaborative ties. Building on efforts in Brazil, Mexico, South Africa, India and China, FIC will expand this effort to include Central and Eastern Europe, Russia and Thailand.

As a fourth emphasis area in 2006, FIC will expand efforts in the neurosciences. With the exception of sub-Saharan Africa, brain disorders are the leading contributor to the years lived with disability in all regions of the world. More than 150 million people suffer from depression at any point in time and nearly one million commit suicide each year. Worldwide, about 25 million people suffer from schizophrenia and 38 million from epilepsy. FIC, in partnership with the National Insti-

tute of Neurological Disorders and Stroke and other NIH Institutes, will continue its efforts to develop new knowledge and technologies to enhance the understanding of brain disorders in resource poor settings around the world. Much of the research funded by this program could have implications for how certain brain disorders are studied, diagnosed, and treated in the United States.

CONCLUSION

The global health challenges we face are many, but the international partnerships supported by Fogarty and its partners are a bedrock upon which scientific progress will be made to the benefit of the American people and the global community.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. THOMAS R. INSEL, DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

Mr. Chairman, and members of the Committee, I am pleased to present the fiscal year 2006 President's budget request for the National Institute of Mental Health (NIMH). The fiscal year 2006 budget includes $1,417,692,000, which reflects an increase of $5,759,000 over the 2005 enacted level of $1,411,933,000 comparable for transfers proposed in the President's request. In my statement, I will call to your attention our Nation's immense burden of mental and behavioral disorders and include a brief review of our research activities and accomplishments.

BURDEN OF MENTAL ILLNESS

The mission of the National Institute of Mental Health (NIMH) is to reduce the public health burden of mental and behavioral disorders. New scientific discoveries and powerful new tools are revealing the mechanisms involved in the pathophysiology of mental disorders. This is a vital step in the development of more effective strategies to manage, treat, and even prevent these debilitating disorders.

The report of the President's New Freedom Commission: Achieving the Promise—Transforming Mental Health Care in America defined the challenge. The burden of these disorders is staggering, in terms of both morbidity and mortality. Mental illness represents 4 of the top 6 sources of disability from medical causes for Americans ages 15–44 according to the World Health Organization; suicide accounts for more deaths each year than either homicide or AIDS. Recent estimates in the President's report put the economic costs of treating mental disorders at $150 billion, with elements of these costs increasing beyond 20 percent per year. The report called for a transformation of mental health care, with recovery as a goal. NIMH is working closely with the Substance Abuse and Mental Health Services Administration (SAMHSA) as it seeks to carry out this mandate.

PRIORITY SETTING

This past year NIMH searched for creative ways in which to optimize its impact on public health; the Institute and its stakeholders endeavored to reevaluate priorities for funding research. To help with this process, two workgroups of the National Advisory Mental Health Council were formed: one to review the NIMH extramural clinical treatment portfolio and one to review the basic sciences research portfolio.

The goal of the clinical treatment workgroup was to help NIMH focus strategically in its support of therapeutics and interventions research. The workgroup's report describes clinical areas where more study is essential, and urges increased innovation and a sharpened focus on amplifying the impact of clinical trials on clinical practice. The report also cites the need to expand core resources and clinical trials infrastructure for NIMH to enhance its treatment development capacity.

The workgroup reviewing the basic sciences research portfolio outlined specific tools and areas of research particularly ripe for increased investment, such as the pathophysiology of mental disorders and the translation of basic science discoveries into biomarkers, diagnostic tests, and new treatments.

Translation of basic science to clinical issues and practice is now a major focus of the Institute. This past year, NIMH reorganized its extramural programs into five research divisions (from three) to focus on: basic science, translational research for adults, translational research for children and adolescents, behavioral effects on health (including HIV/AIDS spread and prevention), and psychiatric services and treatments. A key aim of the reorganization is accelerating translation of the best ideas in neuroscience and behavioral research into the clinics and out into the community.

Rapid advances in mental health research are revealing the biological and environmental components of major mental illness. We now recognize that mental disorders are brain disorders, and we now have the tools to identify the brain circuits involved. Of note is recent research on improved detection of disease with biomarkers and development of personalized treatments.

REVEALING THE BIOLOGICAL BASIS OF MENTAL DISORDERS

A major goal for NIMH is to identify the biological basis of mental disorders to more precisely pinpoint targets for prevention and treatment. This means understanding the neural basis of the illness at all levels, from molecular to behavioral. For instance, imaging studies suggest that ischemia (restriction of blood flow in the brain due to a narrowed or blocked artery) may significantly contribute to the development of a form of depression. In a recent clinical trial, more than half of elderly depressed participants met the criteria for this newly recognized form of depression called "ischemic depression." This realization should help improve diagnosis, and more effectively guide treatment for those with late-life depression.

A recent NIMH study shows that in people with panic disorder, a type of receptor for serotonin (a mood-regulating neurotransmitter) is reduced by nearly a third in several structures of the brain that mediate anxiety. The finding is the first in living humans to show that this specific receptor, which is pivotal to the action of anti-anxiety medications, may be abnormal in the disorder and may help explain how genes might influence vulnerability for panic and anxiety disorders.

A recent translational study on post-traumatic stress disorder (PTSD) was the first to demonstrate in humans the importance of a particular brain region in "fear extinction"—the process by which a previously learned fear is extinguished by a new form of learning, rather than the forgetting of the original fear. The brain region is associated not with emotion, but with the regulation of higher cognitive functions. This will provide important contributions to the understanding and treatment of PTSD and other anxiety disorders.

Several studies on depression have suggested that the formation of new neurons (neurogenesis) might be hindered in those with the disorder. In addition, animal studies have demonstrated that antidepressant medications are likely effective because they help increase neurogenesis. Several genes have been implicated in the susceptibility to schizophrenia and depression. In the past year, we have learned that common genetic variations bias the way the brain works, even in people who have not developed a major mental disorder. For instance, a gene variant that is especially common in people with depression is associated with a higher level of brain activation in response to threat or stress. A variant associated with schizophrenia appears to increase the amount of activity in the frontal lobe needed to perform complex attentional tasks. These kinds of studies reveal how subtle genetic variations may increase vulnerability to mental illness. Ultimately, this may provide a strategy for early detection and prevention of a psychotic or depressive episode based on identifying individuals at genetic highest risk, just as we routinely intervene in those with high blood pressure and high cholesterol to prevent a heart attack.

Autism continues to be an increasing priority for NIH. We are just beginning to see the pay-offs of cross-Institute investments in several new centers and projects. Previous studies show that on average, autism is not diagnosed in children until after the age of 6, a relatively late age considering that early intervention is critical for the best treatment response. Thus, NIMH research will help develop new tools for detecting autism early, before age two. In addition, NIMH is part of a public/private research consortium focusing on the study of infant siblings of children with autism, to help identify early features and distinguishing characteristics of autism. NIMH and other NIH institutes are collaborating with voluntary and private funding organizations and government agencies internationally to develop a new research initiative ($21.5 million over 5 years) to identify specific gene variants that produce susceptibility to autism.

TREATMENTS FOR RECOVERY

The first of several large, NIMH-funded clinical studies testing various treatment options for those with serious mental illnesses was completed last summer: a 13-site trial aimed at defining the most effective and safe treatment for children and adolescents with major depressive disorder. Depression is an important risk factor for suicide, the third leading cause of death among adolescents; it is also a major risk factor for long-term psychosocial impairment in adulthood. There has been much debate about whether a class of antidepressant medications, selective serotonin re-uptake inhibitors (SSRIs) can actually increase suicidal thinking. At

present, fluoxetine (Prozac) is the only FDA-approved medication for depression in children and adolescents, and there have been conflicting results regarding its benefits and risks. The goal of the NIMH trial was to clarify the usefulness of treating adolescent depression with a type of psychotherapy called cognitive behavior therapy (CBT), or fluoxetine, or both. Results of the first 12 weeks found that a combination of fluoxetine and CBT was the most effective treatment (71 percent response rate). Of the other three treatment groups, fluoxetine alone, (60.6 percent response), but not CBT alone (43.2 percent response) was significantly better than placebo (34.8 percent response). Suicidal thinking, which was present in 29 percent of the participants at the beginning of the study, improved significantly in all four treatment groups, with those receiving medication and therapy showing the greatest reduction (below 8 percent). Soon we will know the effectiveness of these treatments over a six-month period from treatment initiation. It is critical for physicians and psychotherapists to closely monitor their young patients on antidepressant medications for signs of hurtful or suicidal behavior, particularly during the early phases of treatment.

A central focus of NIMH treatment research has been finding a more tailored, individual approach to therapy. To personalize treatments, we need to know predictors of treatment response. Recent studies have begun to reveal some predictors that will help clinicians optimize care. For instance, studies of people with major depressive disorder reveal that standard antidepressant medication may be less helpful in those with a history of trauma, or specific genetic variations, or specific patterns of brain activation as seen on imaging scans. These same patients may respond well to cognitive behavior therapy. Similarly, patients with schizophrenia who have poor attentional processing and other cognitive deficits may report less satisfaction with anti-psychotic medications, which were not designed to treat these features of the illness. Ongoing research seeks to find markers that will guide individual treatment to optimize recovery.

Other large trials to be completed within the next year will answer urgent questions about the choice of treatments in people with bipolar disorder, schizophrenia and Alzheimer's, and treatment-resistant major depression. NIMH continues its strong commitment to public dissemination of findings from these clinical trials by fostering partnerships with national and state organizations via the Outreach Partnership Program. Through this program, NIMH works with the National Institute on Drug Abuse and SAMHSA to bridge the gap between research and clinical practice.

BLUEPRINT FOR NEUROSCIENCE RESEARCH

The NIH Blueprint for Neuroscience is a framework to enhance cooperation among the 15 NIH Institutes and Centers that have common interests in the nervous system. By pooling resources and expertise, the Institutes and Centers can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community. The Blueprint is developing a primary set of initiatives including a gateway to existing databases that permits more effective searches; training enhancement for basic neuroscientists; and expansion of ongoing pediatric imaging, gene microarray, and gene expression database efforts.

NIH ROADMAP

NIMH has assumed a lead role on the Molecular Libraries and Imaging initiative of the NIH Roadmap, whose goal is to provide organic compounds called "small molecules" to scientists to use as tools to improve our understanding of biological pathways in health and disease. The potential of scientific discoveries of clinical relevance is enormous. The NIMH mission can be advanced by the identification of even one novel small molecule with biological activity in the brain, as it could provide invaluable information about brain circuits involved in mental illness and those that are altered by treatment.

PREPARED STATEMENT OF DR. STEPHEN I. KATZ, DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The fiscal year 2006 budget includes $513,063,000, an increase of $1,906,000 over the comparable fiscal year 2005 en-

acted level of $511,157,000 comparable for transfers proposed in the President's request.

Improving daily life is the driving force for the research that we support and conduct at the NIAMS. Virtually every home in America is touched by diseases affecting bones, joints, muscles, and skin. We are committed to improving our understanding, diagnosis, treatment, and prevention of these diseases and disorders that are typically costly, chronic, and disabling, many of which disproportionately affect women and minority populations. I am delighted to share highlights of our research progress as well as our plans.

THE NIH ROADMAP FOR MEDICAL RESEARCH

The NIAMS is pleased to partner with other NIH components in the many dimensions of the NIH Roadmap, and the Institute has responsibility for the management of an initiative for a patient-reported outcomes measurement information system—or PROMIS—network. The goal of this initiative is to develop ways to measure patient-reported symptoms such as pain and fatigue and aspects of health-related quality of life across a wide variety of chronic diseases and conditions. The PROMIS initiative will develop a publicly available computerized adaptive test for the clinical research community. Many diseases that compromise daily life involve pain, fatigue, and other difficult-to-measure quality of life outcomes, and the development of a test to measure changes in these symptoms will be of benefit to patients and their health care providers.

RESEARCH IN CHILDREN

When arthritis and other rheumatic diseases affect children, they can significantly compromise a child's ability to enjoy an active life. NIAMS-supported researchers have launched a state-of-the-art genomics project, and the goal of this project is to take full advantage of the tremendous progress that has been realized in genetics and genomics, and to uncover gene expression patterns (groups of genes that are "turned on" or "turned off") that contribute to the development of pediatric arthritis. The NIAMS and a chapter of the Arthritis Foundation and the Schmidlapp Trust are supporting this study of children newly diagnosed with a variety of pediatric diseases such as juvenile rheumatoid arthritis, juvenile ankylosing spondylitis (or spinal arthritis) and other related immune disorders. Identifying the gene expression patterns for different types of arthritis in children will help to improve diagnosis as well as to predict the severity of disease for affected children.

In other studies supported by the NIAMS, the promise of genetic studies was underscored by the identification of a gene variant that increases susceptibility to juvenile arthritis. The NIAMS and the Arthritis Research Campaign funded researchers from around the world who worked collaboratively in collecting DNA samples from children with juvenile rheumatoid arthritis and their parents. Research findings suggest that there may be distinct genetic profiles for the disease that result in differences in age of onset as well as disease severity.

BIOMARKERS OF DISEASE

Progress in identifying the onset and progression of disease is a challenge in many chronic diseases, and the NIAMS has taken the lead in three initiatives to address this challenge: the first is the Osteoarthritis Initiative—a public-private partnership that the NIAMS, the National Institute on Aging, several other NIH components, and three pharmaceutical companies support that is working to develop clinical research resources for the discovery and evaluation of biomarkers and surrogate endpoints for clinical trials on osteoarthritis (the most common form of arthritis). Data and images collected will be available to researchers around the world to speed the pace of research in biomarker identification, and this consortium is expected to serve as a model for initiatives in the future that involve public and private partnerships. We have already enrolled 1,900 individuals to participate in this Initiative. The second initiative is the creation of the Osteoarthritis Biomarkers Network involving institutions in the United States and Sweden. This Network facilitates the sharing of clinical, biological, and human resources to more rapidly and more effectively identify biomarkers for osteoarthritis. In the third biomarker initiative, the NIAMS supports the Autoimmune Biomarkers Collaborative Network which includes efforts to identify and validate biomarkers for lupus—a serious and potentially fatal autoimmune disease that occurs with greater frequency and intensity in African American women, and that affects many organ systems of the body.

ARTHRITIS AND OTHER RHEUMATIC DISEASES

Rheumatoid arthritis is an autoimmune disease, and affected individuals often must be treated with powerful drugs that may help to keep the disease better controlled, but also suppress the immune system—leaving patients particularly vulnerable to infection. NIAMS-supported researchers have identified a potential treatment that will suppress the abnormal, autoimmune response that causes the rheumatoid arthritis, but does not diminish the patient's ability to fight bacteria and viruses. The treatment is a synthetic peptide (a chain of amino acids) called dnaJP1—a particular section of a protein that has the same characteristic amino acid sequence as that found in patients with rheumatoid arthritis. In initial studies a synthetic version of the dnaJP1 peptide was given to patients with rheumatoid arthritis with the goal of blocking the immune response, and the immune system responses were normal in these treated patients. The NIAMS partnered with the National Institute of Allergy and Infectious Diseases, the Royal Netherlands Academy of Arts and Sciences, and the Dutch Organization for Scientific Research in funding this study. A new larger study will be undertaken to pursue studies of this promising synthetic peptide for people with rheumatoid arthritis.

Fibromyalgia is a disease that affects many systems of the body, affects women far more commonly than men, and is characterized by low pain thresholds at specific tender points in the body. NIAMS-supported researchers have furthered our understanding of fibromyalgia in recent studies that determined that fibromyalgia was strongly aggregated in families, and that the number of tender points as well as total muscle pain scores were strongly associated with fibromyalgia in families. In addition, there was an increase in the presence of mood disorders in relatives of fibromyalgia patients. This aggregation of fibromyalgia in families suggests that genetic factors may play an important role in this disease. The NIAMS supported a workshop in November 2004 that reviewed the state of the science and a view to future studies in fibromyalgia.

BONE AND MUSCULOSKELETAL DISEASES

Osteoporosis is characterized by bone thinning that results in increased susceptibility to fracture. A particular clinical challenge has been that often the first indication of osteoporosis is when a person (most often a woman) has a bone fracture, and by then the bone has already thinned. Better methods are needed to screen for osteoporosis and for those who are at high risk for fractures. Researchers have recently learned that bony regions of conventional dental x-rays may be useful in evaluating both the current micro-architecture of bone as well as following changes in bone over time. Bone quality plays a critical role in osteoporosis and other bone diseases, and the NIAMS has partnered with the American Society for Bone and Mineral Research in sponsoring a meeting in May 2005 to evaluate the current status of assessment methods to serve as surrogates for fracture and bone fragility, as well as to determine the next steps that must be taken to validate these methods and incorporate them into clinical trials. In other studies with relevance for osteoporosis, basic scientists have identified a particular gene (Alox15) that is strongly associated with changes in bone mineral density—a measure of vulnerability for osteoporosis. Researchers had previously identified the involvement of Alox15 in fat metabolism, so the identification of its role in bone links metabolic pathways and bone changes, and also provides a new drug target for osteoporosis.

MUSCLE DISEASES

One of the most active and productive areas within the Institute's research portfolio is in the muscular dystrophies—a group of genetic diseases characterized by progressive weakness and degeneration of the skeletal or voluntary muscles which control movement. NIAMS research has made progress in defining the genetic mutations and in overcoming the current barriers to effective gene therapy of Duchenne muscular dystrophy, Facioscapulohumeral dystrophy, and other muscle diseases. For example, scientists supported by the NIAMS and the Muscular Dystrophy Association recently reported that a particular method of gene therapy was able to reach all damaged muscles in a muscular dystrophy (MD) mouse, with implications for delivering genetic therapy for MD and perhaps other diseases of the muscle or heart. Previous work showed that MD could be prevented from occurring in a mouse model of the disease by replacing the gene for dystrophin, which is defective in people with the Duchenne form of the disease with a corrected copy of the gene. However, until now, no one had found a way to deliver a new gene to all muscles of an adult animal, including muscles that had already developed MD.

The NIAMS has teamed with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Child Health and Human Development (NICHD) to bring a strong focus to basic and clinical studies of MD. Activities include the efforts related to the new Muscular Dystrophy Coordinating Committee (MDCC), and the Muscular Dystrophy Research and Education Plan for the NIH that was developed by the MDCC and released in September 2004. In addition, in fiscal year 2003, the NIAMS, along with NINDS and NICHD, each funded a Muscular Dystrophy Cooperative Research Center for which additional funding was provided by the Muscular Dystrophy Association. In fiscal year 2004, the three institutes re-issued the solicitation for centers—now known as Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, and expect to fund two to three additional meritorious centers in fiscal year 2005.

The NIAMS, NINDS, NICHD and the Centers for Disease Control and Prevention sponsored a workshop on the burden of muscle diseases in January 2005. The participants in this workshop identified existing data on the costs and scope of muscle diseases, with a focus on the muscular dystrophies, and recommended strategies for developing new information sources.

SKIN DISEASES

Skin diseases significantly compromise daily life for millions of Americans, both physically and psychologically. Researchers supported by the NIAMS have made great progress in our understanding of basic skin biology as well as understanding the bases for skin diseases.

A particular area of focus in the NIAMS portfolio is on the roles of genes in skin diseases, and scientists have advanced our understanding in a number of areas, including identifying two genes on chromosome 17 which are associated with psoriasis. Other studies have identified susceptibility genes for keloids, which are an abnormal form of scarring that disproportionately affects people of color. Investigators studying the physiologic basis for keloid formation were able to determine that a blood vessel growth factor was likely to be associated with keloid formation. This suggests that it may be possible to suppress keloid formation by topical application of an inhibitor of this molecule. In a third area of genetics research, investigators have identified a new mouse model of alopecia areata that has allowed genetic susceptibility studies to be undertaken, and two new regions on chromosomes 8 and 15 were identified. The availability of this new animal model will allow better identification of the genetic basis of alopecia areata as well as provide a basis for testing potential interventions.

CONCLUSION

Significant progress has been made in our understanding of fundamental life processes and how they go awry in diseases of bone, joints, muscles, and skin. We are proud of the advances that scientists supported by the NIAMS have achieved, and we are excited about initiatives that we have launched. Our goal remains, as always, to improve the health of the American public—to reduce the burden of disease and to enrich the quality of life for all Americans.

I will be happy to answer any questions that you may have.

PREPARED STATEMENT OF DR. TING-KAI LI, DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The fiscal year 2006 budget includes $440,333,000, which reflects an increase of $2,056,000 over the fiscal year 2005 enacted level of $438,277,000 comparable for transfers proposed in the President's request. The Centers for Disease Control and Prevention last year ranked alcohol the number-three preventable cause of death in the country. This finding echoed a report issued by the World Health Organization, which listed alcohol as the third leading preventable cause of healthy years lost to death and disability in developed nations during 2002. The high rate of death and disability associated with alcohol is the result not only of injury, but also of organ damage, including brain damage. Alcohol's biological actions are widespread in the body, and, when used in excess, it has the potential to contribute to conditions such as cancer and liver disease. Every age group is at risk of alcohol-related problems, from fetuses exposed to alcohol in the womb to the elderly. In the United States, the estimated annual cost of alcohol-use disorders (al-

cohol abuse and alcohol dependence), including indirect costs, such as lost productivity, is $185 billion.[1]

MEDICATION DEVELOPMENT

Development of more widely effective medications for alcohol-use disorders and organ damage is among NIAAA's highest priorities; it is among the 28 research outcome goals listed in the NIH Government Performance and Results Act report. Medications help prevent or reduce drinking by acting on one or more of the many brain systems through which alcohol exerts its actions. For example, some medications reduce craving for alcohol. We are testing promising compounds for treatment of alcohol-use disorders, by themselves and in combination with behavioral therapies, and for treatment of liver damage.

Recent advances in science and technology have enabled remarkable progress in our understanding of neurobiological mechanisms that underlie behavior, and are revealing new molecular targets for medications for alcohol-use disorders. Likewise, advances in our understanding of organ injury are providing new opportunities for developing medications. These advances are reflected in unprecedented progress in NIAAA's medication development initiative.

A special challenge for our initiative is to develop strategies that will increase translation of promising medications identified by NIAAA research into clinical applications. The pharmaceutical industry has been reluctant to develop medications for alcoholism, and the medical community has been reticent to use new pharmacotherapeutic modalities as an adjunct to traditional behavioral therapies for the treatment of this disease. For example, only 3 to 13 percent of patients treated for alcoholism receive a prescription for the medication naltrexone, although it has yielded positive results in NIAAA-funded studies published in medical journals. We need to increase the likelihood that compounds we identify as effective and safe will reach the market and that they will reach patients who can benefit from them. Research is underway to identify barriers and strategies to remove them.

Our recently established collaboration with the Food and Drug Administration (FDA) will help to expedite progress. Together, NIAAA and FDA are developing standards for clinical trials of medications to be tested as alcoholism treatments. This will help ensure that NIAAA-supported trials are in line with regulatory requirements, enabling them to proceed.

Our two highest priorities for accelerating our medication program are (1) to develop animal models and human research paradigms that can predict the clinical success of potential medications. Having these predictive models in place will prevent spending time and money on more elaborate testing of compounds that would ultimately fail to be effective. (2) Another priority is to establish a network of sites for early stages of human testing of medications, to reveal whether or not a drug should be pursued in larger, more expensive trials. Medications in this system will be on a fast track, in which scientific elements of safety testing, etc., remain, but elimination of unnecessary administrative roadblocks will expedite the process.

IN THE PIPELINE

Human trials of two particularly promising medications are underway. Among the studies being conducted is a collaboration with the National Institute on Drug Abuse (NIDA), to test the antiseizure drug topiramate's effectiveness in treating people addicted to both alcohol and cocaine. Antiseizure drugs act on neurotransmitter systems that modulate brain-cell activity, to restore their natural balance. Alcohol causes an imbalance in the glutamate and GABA neurotransmitter systems (among others) and topiramate's actions on these receptors are thought to ease some of the symptoms of alcohol withdrawal. The drug rimonabant is directed at a different neurotransmitter system (the cannabinoid system) and has shown considerable promise in animal studies. Several other kinds of medications that have shown promise in research settings are in various phases of clinical studies, including several collaborations with other NIH Institutes.

---

[1] Harwood, H.; Fountain, D.; and Livermore, G. (2000). The Economic Costs of Alcohol and Drug Abuse in the United States 1992 (updated for 1998). Report prepared for the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services. NIH Publication No. 98–4327. Rockville, MD: National Institutes of Health. NIAAA's mission is to develop prevention and treatment interventions that reduce alcohol-use disorders and their consequences. To achieve this goal, we must understand the underlying biological, behavioral, and environmental factors and identify populations at risk. NIAAA research initiatives in four areas, in particular, are essential to this effort: medication development, neuroscience, metabolism, and youth.

Some populations are at particular risk, and we also are conducting studies specific to them. We are testing medications in youth, who have high rates of alcohol abuse. This group poses special challenges, since the biological changes that occur in the brain during adolescence might compromise the pharmacologic actions of medications used for adults.

People with co-occurring alcoholism and psychiatric conditions are another high-risk group. Our studies of this population include collaborations with the National Institute of Mental Health. In a recent trial, a drug already used as an anticonvulsant and to treat bipolar disorder showed promise in treating alcoholism in bipolar people, who are generally resistant to current medications for alcoholism.

A collaboration with the National Cancer Institute and NIDA is helping researchers to understand the biological interactions that occur between alcohol and nicotine, and to develop treatments for alcoholic smokers. Studies suggest that addiction to alcohol and nicotine involves some common underlying mechanisms.

In addition to developing medications to treat alcohol-use disorders themselves, we are developing treatments for alcoholic liver disease. Alcohol is among the leading causes of death from liver disease in the United States.

Pharmaceutical companies put aside many of the medications they develop. Even though they may be safe, they may not be optimally effective for treating the diseases or conditions for which they were developed. These medications are potentially useful for treatment of other diseases, and some act on neurotransmitters that we have identified as promising targets for treatment of alcoholism. We are encouraging pharmaceutical companies to collaborate with us in developing these compounds as potential alcoholism treatments.

NEUROSCIENCE AND METABOLISM

The biology of the brain contributes to how we make decisions—to the choices we make in life and the behaviors in which they result. Neuroscience research is essential for understanding the biological basis of alcohol-related behaviors and for identifying molecular targets for therapeutic compounds that can alter alcohol's actions in the brain. Many different biological systems in the brain influence how people respond to alcohol, and chronic, heavy exposure results in brain adaptations that form the underpinnings of alcoholism.

NIAAA-funded scientists are making important discoveries about genes and proteins active in these brain systems, whose variant forms increase or decrease the risk of alcohol-use disorders. For example, recent studies suggest that a gene that produces an appetite-regulating protein fragment, neuropeptide Y, also affects tolerance to alcohol, a predictor of alcoholism and a factor in its development.

In 2006, NIAAA will take part in the NIH Blueprint for Neuroscience, a collaboration of 15 Institutes. We are particularly interested in the Blueprint's cross-training programs for the next generation of researchers and clinicians in neuroscience. One component trains physicians and scientists to work together toward translating neuroscience findings into clinical practice; others provide training in computer and neuroimaging technologies that offer unprecedented research capabilities. The Blueprint's project to target all of the genes in the mouse genome, to discover which of them are critical players in health or diseases of the nervous system, will benefit NIAAA research.

Metabolism also has a profound effect on people's responses to alcohol. Variations in the genes and proteins involved in alcohol metabolism can, like those involved in brain function, increase or decrease risk of alcoholism. NIAAA's metabolism initiative is making progress in identifying these gene/protein variations and their impact on alcohol-related behaviors, particularly in regard to enzymes in alcohol-metabolism pathways. The NIH Roadmap Initiative on National Technology Centers for Networks and Pathways is contributing valuable information to the effort. Like our neuroscience research, our metabolism research is helping us to identify potential targets for therapeutic compounds.

YOUTH AT RISK

Last year, we reported that new epidemiology data called for a major scaling up of efforts to prevent underage drinking. The data revealed that youth is the age of greatest risk of alcoholism; people 18-to-25 years old have much higher rates of alcoholism than any other age group in the Nation. Previous studies had shown the extent to which youth engage in risky patterns of drinking, such as occasionally or frequently drinking too much, too fast. Alcohol is the largest contributor to unintentional injury, the leading cause of death of Americans under age 21. People who begin drinking earlier in adolescence have a much higher risk of alcoholism as adults, as compared with late starters. Children are beginning to drink at earlier

ages, and youth from secondary-school age to college age have substantial rates of risky drinking. In the military, more than 26 percent of underage personnel engage in "binge drinking" (five or more drinks in a row), according to a recent Department of Defense report. These and other epidemiology data indicated to us that (1) the problem of underage drinking required renewed emphasis and coordination in the research and service communities, and (2) we should approach alcoholism as having a developmental trajectory that begins in childhood and adolescence. In a recent report, *Reducing Underage Drinking: A Collective Responsibility*, the Institute of Medicine called for strategies to ameliorate these problems. Last year, NIAAA announced the addition of a major new initiative to its ongoing research on youth.

YOUTH INITIATIVE

Research shows that brain development and maturation occur over a longer period than previously thought. A key question we are asking is: What brain systems differ in adolescents and adults such that youth tend to binge drink? The brain receives and sends chemical messages that influence when an individual has "had enough" and stops drinking. Are the brain systems that regulate these "stop mechanisms" not yet mature in the adolescent brain? Does alcohol alter their development? A collaboration with NIDA is stimulating studies on consequences of alcohol exposure and drug abuse on development of the brain and behavior.

NIAAA has formed a steering committee that includes both scientists and policy and communication experts. The former chairman of the IOM committee on underage drinking is a member, as are two of the 60 current and former governors' spouses leading a national NIAAA-sponsored prevention campaign. In addition, the NIAAA sits on the newly established Interagency Committee on Prevention of Underage Drinking. This Committee cuts across agencies, from research to service, including the Substance Abuse and Mental Health Services Administration, in a major coordination of effort.

Our initiative also is reaching out to health-care systems and communities. An area in critical need of attention is the response of health care systems to underage drinking. NIAAA's youth initiative is beginning to address this need, in part, with a project called *Underage Drinking: Building Health Care System Responses*. Rural academic health centers will use existing services and clienteles to conduct the studies.

The youth initiative is responding to crisis levels of risky drinking on college campuses, as well. It includes fast-track approval of grant applications in response to campuses that request help, a recommendation issued in the NIAAA Task Force on College Drinking—a collaboration between scientists and college presidents. Seven approved and funded projects are underway; another application is nearing approval, and others are under review. The Task Force is about to release an updated report, which will reflect the latest research findings. Another new program under the youth initiative, the Mississippi River Delta Project, is examining whether a prevention strategy recommended for college students by the Task Force is effective for rural adolescents.

One major question that must be addressed regarding underage drinking and its consequences is whether enforcement of existing laws can reduce these problems by reducing youths' access to alcohol. We recently began collaborating with the Office of Juvenile Justice and Delinquency Prevention to address this question in rural communities. NIAAA's role in this joint effort is to provide the research required for evaluation of the effectiveness of the 3-year program. Four projects are underway; three more are nearing approval.

The leadership of the youth initiative is discussing collaborations with other potential partners. In Spring 2005, we will meet with leaders in the radio and television media about the effects of alcohol portrayal on youth behaviors. Navy leaders have requested a meeting with NIAAA, also to be held in Spring 2005, to discuss prevention and treatment strategies. We have begun discussions with the Department of Agriculture about the possibility of conducting research and outreach through the 4–H Club organization.

AT THE CROSSROADS

The results of our research will be useful to the public to the extent that clinicians and communities apply them. We are at a crossroads, in which we are able to identify new medications, for example, while the pharmaceutical and medical communities are relatively unresponsive to new findings in alcohol research, and prevention and treatment are not reimbursed adequately by private insurers.

At this juncture, a high priority for our Institute is to develop strategies that will increase the likelihood that clinicians, communities, and health-care systems will

adopt findings from our investigations. Efforts are underway. Thank you Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. STORY C. LANDIS, DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Mr. Chairman and Members of the Committee I am Story Landis, Director of the National Institute of Neurological Disorders and Stroke (NINDS). I am pleased to present the fiscal year 2006 President's budget request for NINDS. The fiscal year 2006 budget includes $1,550,260,000, an increase of $10,812,000 over the fiscal year 2005 enacted level of $1,539,448,000 comparable for transfers proposed in the President's request.

The mission of the NINDS is to reduce the burden of neurological disorders by finding ways to prevent or to treat these diseases. This mission is extraordinarily important and extraordinarily difficult. It is important because the burden of neurological disorders is immense, affecting all segments of society. Diseases of the nervous system kill people of all ages, disrupt essential bodily functions, cause pain and discomfort, and disturb all aspects of human ability, from perception and movement through emotions, memory, language, and thinking. It is difficult because hundreds of diseases affect the brain, spinal cord, and nerves of the body, each presenting unique challenges. Compounding the challenge, the brain and spinal cord are difficult to access, sensitive to intervention, reluctant to regenerate following damage, intricate in structure, and elusive in their normal workings.

Despite these challenges, we are making progress. Prevention of stroke and of nervous system birth defects is having a major impact on public health. Better drugs and surgical treatments help relieve symptoms for people with Alzheimer's disease, Parkinson disease, epilepsy, chronic pain, multiple sclerosis, and other diseases. Improvements in genetic testing and brain imaging also enhance physicians' ability to diagnose disease and guide therapy for nervous system disorders.

To continue this progress, the NINDS supports basic studies to understand the nervous system in health and disease, translational research to move from the laboratory toward the clinic, and clinical research, including clinical trials to test the safety and efficacy of treatments and preventive interventions. The Institute supports most research through extramural grants and contracts to physicians and scientists throughout the country. NINDS intramural investigators also conduct research on the NIH campus in Bethesda, Maryland.

To complement investigator-initiated research, the Institute directs initiatives to public health needs, unusual scientific opportunities, or issues that Congress highlights as critical. NINDS initiatives for fiscal year 2006 focus on tuberous sclerosis, Rett syndrome, muscular dystrophy, neuro-AIDS, transmissible spongiform encephalopathies (TSEs), stroke, and Parkinson disease, as well as on cross-cutting issues including counterterrorism, neurological emergencies, and stem cells. Increasingly, NINDS initiatives and other programs are in cooperation with other components of the NIH.

CLINICAL RESEARCH

The NINDS currently supports more than 1,000 research projects that involve human subjects, with more than 300,000 people expected to participate. For example, epidemiological studies are examining risk factors for stroke with special attention to Blacks and Hispanics; genetic studies have recently helped identify genes related to Parkinson disease, ALS, dystonia, Joubert syndrome, and cerebrovascular disease; and brain imaging research is revealing how the brain develops throughout childhood and adapts after damage. Among the findings this year are brain imaging data that will identify which stroke patients might benefit from emergency treatments to unblock blood vessels and preliminary indications that vitamin D might help prevent multiple sclerosis in women, a finding which researchers are following up.

Of the NINDS clinical research studies, approximately 125, with more than 25,000 expected participants, are clinical trials of interventions to prevent or treat neurological disorders. Projects range from planning and pilot trials to large multicenter trials. In notable results this year, a small intramural clinical trial of multiple sclerosis patients who did not respond to interferon, the standard therapy, found that administering the genetically engineered antibody daclizumab improved outcome substantially. An extramural clinical trial found that ultrasound may improve the effectiveness of t-PA (tissue plasminogen activator) in breaking up clots and restoring blood flow to the brain. T-PA has been the only FDA-approved ther-

apy for acute ischemic stroke since NINDS clinical trials demonstrated its effectiveness in the 1990's.

In other clinical trials activities this year, the innovative Neuroprotection Exploratory Trials in Parkinson Disease (NET-PD) program is selecting drugs that show promise for slowing the course of Parkinson disease and testing them through a clinical trials network. From 59 drug candidates proposed by 42 scientists from 13 countries, 4 drugs were selected for testing in phase II clinical trials, with results expected in the next few months. If results warrant, larger trials will follow quickly. To enhance drug selection in the future, the NINDS is establishing a contract animal testing facility. The NINDS Pilot Studies Network (NPTUNE) is also underway to expedite pilot trials of new treatments for rare neurological disorders, for which the lack of clinical trials infrastructure often blocks moving therapies forward. NPTUNE chose testing of phenylbutyrate for spinal muscular atrophy (SMA) as the first trial. Development of the Clinical Research Collaboration (CRC) has also begun, which will extend the reach of the NIH into more communities across the United States. The CRC will engage hundreds of community practice and academic neurologists to speed trials; minimize costs; make trials more accessible to patients; recruit a diverse spectrum of participants; facilitate trials of rare diseases; and improve transfer of research results to clinical practice in community settings. Complementing the CRC, the NINDS is building a network to develop emergency treatments for neurological disorders. Stroke, seizures, and traumatic injury are just a few of the neurological disorders that often require emergency treatment. This program brings together specialists in emergency medicine with experts in neurological disease and in clinical trials. Finally, the NINDS is fully engaged in Roadmap initiatives to address clinical research and trials issues that cut across all of medical science.

TRANSLATIONAL RESEARCH

Translational research encompasses the many steps that move basic research findings to a therapy that is ready for testing in clinical trials. In 2002, the NINDS began a comprehensive translational research program that can apply to all diseases within its mission. The program solicits investigator-initiated proposals, evaluates them according to peer review criteria tailored to the needs of translational research, and monitors progress with milestone-driven funding, as is common in industry. The first major project in this program, the Parkinson's Gene Therapy Study Group, met critical milestones this year with the creation of a stable colony of parkinsonian non-human primates for testing therapies and the development of modified viral vectors that can deliver therapeutic genes under tight control.

Complementing the broad translational research program and relevant Roadmap initiatives in areas such as molecular libraries are several specific NINDS efforts. In one such program, the Institute, working with academia and voluntary disease organizations, formed a consortium of 26 laboratories to screen a set of 1,040 known drugs with laboratory tests for potential use against neurodegenerative diseases. Most of the drugs in this set have been approved by the U.S. Food and Drug Administration (FDA) for other uses, and so might move more quickly toward clinical trials. Several drugs from this program have shown promise against neurodegeneration and moved forward to testing in more definitive mouse models of human diseases. One drug, ceftriaxone, has already proceeded to testing in a clinical trial for ALS early this fall.

Because of the state of the science and the impact of SMA on children and families, the NINDS chose this disease as the focus of an innovative approach to expedite therapy development. The SMA Project uses a performance-based contract mechanism to accelerate all steps from recognition of a research need, through solicitation, review, and funding of targeted research subprojects. In its first year, the Project quickly developed detailed plans for SMA drug development and solicited targeted research subprojects. A September 2004 workshop engaged SMA researchers, clinicians, and voluntary health organizations on clinical trials. As the Project proceeds, the NINDS is evaluating whether the approach might be applied to other disorders. The NINDS continues to support teams of researchers focused on developing therapies for neurological diseases through several other programs. These programs emphasize basic, translational, or clinical research, as appropriate to the state of science for each disorder. Examples include the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, the Morris K. Udall Centers of Parkinson's Disease Research, the Facilities of Research Excellence in Spinal Cord Injury, and the Specialized Programs of Translational Research in Acute Stroke.

BASIC RESEARCH

Preventing and treating neurological disorders relies on understanding the normal workings of the nervous system and what goes wrong in disease. The emerging new modalities for combating disease highlight this: Stem cells and growth factors arose from fundamental studies of nervous system development. Deep brain stimulation, which shows promise for Parkinson, dystonia, Tourette syndrome, and other diseases, relies upon research techniques developed to monitor the activity of single nerve cells in the brain, and on basic knowledge of anatomical circuits that control movement. Studies of how the brain learns are leading to behavioral therapies that may enhance "brain plasticity" to repair damage and giving new insights into what causes chronic pain, epilepsy, and dystonias. Most current drugs for nervous system diseases target molecules identified for their role in normal brain function. Gene therapy, new understanding of the molecular basis of diseases, diagnostic tests, and animal models for testing therapies are among the many fruits of fundamental studies in neurogenetics.

Basic neuroscience research is continuing to advance rapidly, and Roadmap initiatives in areas such as protein structure, computational biology, and nanomedicine will help to accelerate that pace. Among the many basic neuroscience findings this year are studies that give insights into what controls stem cells in the brain and how they might be used therapeutically, the role of estrogen in autoimmune disease, strategies to transfer therapeutic genes into muscles to treat dystrophies, insights into the molecular targets of nicotine, better understanding of how genes and experience interact in brain development, and a new approach to silencing harmful genes in diseases such as Huntington's and spinocerebellar ataxias.

THE NIH BLUEPRINT FOR NEUROSCIENCE RESEARCH

Over the last several years, the NIH Institutes and Centers that have an interest in the nervous system have increasingly joined forces, driven by advances in neuroscience that have revealed common issues that intersect their unique missions. The NIH Blueprint for Neuroscience is a framework to enhance that cooperation. Just as the NIH Roadmap addresses the roadblocks that hamper progress across all of medical science, the NIH Blueprint for Neuroscience takes on challenges in neuroscience that are best met collectively. By pooling resources and expertise, the 15 NIH Institutes and Centers that make up the Blueprint can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community. The Blueprint is developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives include an inventory of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of ongoing pediatric imaging, gene microarray, and gene expression database efforts. For fiscal year 2006, Blueprint initiatives focus on genetically engineered mouse strains to study the nervous system, neuroscience training programs, and specialized "core" resources that can be shared across many laboratories.

Thank you, Mr. Chairman. I would be pleased answer questions from the Committee.

PREPARED STATEMENT OF DR. DONALD A.B. LINDBERG, DIRECTOR, NATIONAL LIBRARY OF MEDICINE

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Library of Medicine (NLM). The fiscal year 2006 includes $318,091,000, an increase of $2,945,000 over the fiscal year 2005 enacted level of $315,146,000 comparable for transfers proposed in the President's request.

In a world that is increasingly digital, the National Library of Medicine plays a pivotal role in facilitating research, supporting safe and effective health care, and promoting healthy behavior. In addition to maintaining the largest physical collection of health science literature in the world, the Library builds and makes freely available immense databases of scientific information, identifies and organizes free Web-based consumer health information produced by the NIH institutes and other authoritative sources, and connects all of these resources in novel ways that increase their value to scientists, health care practitioners, and the general public. Each day, almost a million people access the National Library of Medicine's digital resources. By making the results of research—from DNA sequences to published sci-

entific articles to patient and consumer health information—readily available, the Library magnifies the positive impact of NIH's investment in the creation of new knowledge.

The Library is a key player in a number of important NIH and HHS initiatives that have current implications for the scientific community, health care providers, and the general public. These are described later, but briefly they are: the new policy to encourage the depositing of peer-reviewed articles supported by NIH grant in an archive maintained by the Library; the creation of PubChem, a new resource for scientists that is part of the NIH Roadmap Initiative; the movement to widen the registration of clinical trials in ClinicalTrials.gov, an NIH/NLM database; and the dissemination of standard vocabulary for electronic health records and research data within NLM's Unified Medical Language System (UMLS).

INFORMATION FOR SCIENTISTS AND HEALTH PROFESSIONALS

The Library's services have never been more central to the scientific enterprise. No scientist would think of embarking on an experiment without a careful review of the literature. Researchers rely on NLM databases for this. They search the Medline/PubMed collection of 15 million journal article records, or perhaps utilize the GenBank collection of 40 million DNA sequences and associated molecular data. Research articles and biological databases are interlinked through NLM's Entrez retrieval system that provides seamless searching of a vast information space all from a user's desktop computer.

The original role of the Library, to provide access to the published literature of the health sciences, remains the foundation of NLM's services, and the physical collection continues to expand steadily. Medline/PubMed is a Web-accessible database that now contains more than 15 million references and abstracts to articles in biomedical journals from the 1950s to the present. For most of the records now being entered, it is possible to link from the reference to the full text of the article. More than half a million records, from journals in many languages, are added each year. Medline/PubMed is free on the Web and in fiscal year 2004 there were 678 million searches done on the system.

PubMedCentral, which was created by NLM's National Center for Biotechnology Information (NCBI), is a database that is a key in one of the special NIH initiatives mentioned earlier—archiving the full text of articles that represent work supported by the NIH. Today's technology has led to research that frequently generates an enormous amount of data that is associated with the publication of an article. To maximize the usefulness of such articles, the full text needs to be stored, with ancillary data, and with links to associated resources, in a data repository such as PubMedCentral. Under a new NIH policy, peer-reviewed research articles are submitted electronically to PubMedCentral. There are now more than 350,000 current and retrospective articles available free of charge in this archive.

NLM's NCBI also hosts over 40 databases providing researchers and students with easy access to molecular biology information—sequences, genome maps, 3-D protein structures, and gene functions. The integration of all these data coupled with Web-based analysis tools offers a virtual desktop laboratory to the 50,000 researchers and students who visit daily over the Internet.

With the completion of the NIH genome project, an important new opportunity to explore the interactions of chemical substances with biological systems has opened. The Molecular Libraries component of the NIH Roadmap aims to exploit this opportunity by developing chemical probes that modulate biological processes. A new database created by the NCBI, called PubChem (the second major initiative noted earlier), integrates data from a variety of sources to enable researchers to link diverse information about chemicals and biological processes. For example, PubChem links chemicals to PubMed, so that users may investigate the relationship of screening-center results and biological activities reported in the biomedical literature. As such, PubChem is a research tool for expediting discovery of the biological basis of disease and the development of new therapeutic approaches.

A new information system was introduced by NLM in 2004: the Wireless Information System for Emergency Responders (WISER). Available for downloading over the Internet, the system uses a hand-held PDA device to provide on-the-spot information for emergency personnel who first respond to situations where hazardous materials have been released into the environment. WISER extracts data from NLM's extensive electronic file of peer-reviewed hazardous substances information and makes it instantly and conveniently available.

INFORMATION SERVICES FOR THE PUBLIC

The Library was first prompted to create information services for the general public in 1997, when it became apparent that consumers were in fact using the Medline/PubMed database of the scientific medical literature heavily. The following year the NLM Board of Regents formally recommended that the Library expand its mandate to include serving the public. Since that time, NLM has created a series of highly successful Web-based information services aimed at consumers.

Foremost among these is MedlinePlus.gov. This service, begun in 1998, has become a much-consulted information resource for the public, patients, and their families. Some 6 million people use MedlinePlus each month, viewing more than 60 million pages of health information written especially for consumers. Much of the data comes from the NIH institutes, a reliable source of authoritative health information for the public. Other HHS health agencies, professional societies, voluntary health agencies, and academic organizations are also sources of the information carried on MedlinePlus. Many users come to the site for access to extensive information on prescription and over-the-counter medications, a medical encyclopedia, directories of physicians and hospitals, and "health tutorials" on common medical topics and procedures.

With help from the medical library community and from the National Institutes of Health, MedlinePlus continues to expand its coverage. A "Go Local" function has been introduced so that users of MedlinePlus can link directly to organizations and agencies in their locality to request needed health services. North Carolina and Missouri are now connected locally, and more states will soon be joining Go Local. Another popular service is MedlinePlus en español. This was introduced in 2002 and has grown rapidly to reach virtual parity with the English version. Both English and Spanish language MedlinePlus scored the highest marks of any Federal Web site in a recent evaluation by the American Customer Satisfaction Index.

One popular feature of MedlinePlus is the ability to link from any of the health topics to the database, ClinicalTrials.gov. In the past, information about clinical research was not readily available to the public. Patients typically learned about studies only from their doctors. ClinicalTrials.gov, which now contains extensive information on more than 12,000 studies, is a one-stop Web site for patients, families, and members of the public. Each record includes the locations of a study, its design and purpose, criteria for participation, contact information, and further information about the disease and intervention under study. One of the special NIH initiatives mentioned at the beginning of this statement is about the need for a broad registry to track all trials and their results. Because ClinicalTrials.gov provides an established system for collecting, organizing, and displaying study information, expansion of its role is being considered.

In addition to MedlinePlus and ClinicalTrials.gov, the Library in recent years has introduced a number of specialized information resources for different segments of the public. NIHSeniorHealth.gov, for example, created with the National Institute on Aging, has information in a format that is especially usable by seniors on topics they are concerned with, such as Alzheimer's, arthritis, hearing loss, exercise for older adults, and so forth. There are other information resources created by NLM especially for people living with AIDS, American Indians, those living in the Arctic, and Asian Americans.

The public will also find useful NLM databases that contain health and safety information about the content of everyday household products, consumer information about genetic conditions and the genes or chromosomes responsible for those conditions, and the potential environmental hazards in ordinary communities ("Tox Town"). The newest database of interest to the public is TOXMAP, a system that allows the user to specify a chemical, or a location, and to create a map that shows the distribution of that chemical in a geographic area.

The usage of the Library's databases, both those for scientists and for the public, continues to climb. NLM pursues a number of outreach projects to spread the word that these resources are available to everyone, free and without registration. The more than 5,000 member institutions of the National Network of Libraries of Medicine are valued partners in this endeavor. They hold workshops at public libraries and other community organizations, demonstrate NLM databases to the public, and exhibit at meetings and conventions on behalf of NLM, thus providing the personal element that can be so important to reaching populations affected by health disparities. Another special outreach project is the "Information Rx" program, a collaboration with the American College of Physicians (ACP) Foundation. This is a project to encourage physicians to make information referrals to MedlinePlus. Since patients trust their physicians to recommend good health information, the idea is to promote MedlinePlus as the "Web site your doctor prescribes." NLM is also now

working with the American Medical Association Foundation in a similar project for its members.

RESEARCH TO IMPROVE INFORMATION PRODUCTS AND INFRASTRUCTURE

In addition to the work of the National Center for Biotechnology Information, described earlier, NLM also sponsors research and development through the Lister Hill National Center for Biomedical Communications. This organization conducts advanced communications research projects in such areas as high-quality imagery, medical language processing, high-speed access to biomedical information, developing intelligent database systems, multimedia visualization, data mining, and machine-assisted indexing. One prominent area of research has been the Visible Human Project. The project consists of two enormous (50 gigabytes) data sets, one male and one female, of anatomical MRI, CT, and photographic cryosection images. These data sets are available through a free license agreement. More than 2,000 individuals and institutions in 47 countries have licensed the data and are using them in a wide range of educational, diagnostic, treatment planning, virtual reality, artistic, and industrial applications. An "Insight Toolkit" makes available a variety of open source image processing algorithms for computing segmentation and registration of medical data. The Visible Human Web site is one of the most popular of NLM's Web offerings.

Another initiative of the Lister Hill Center is the Scalable Information Infrastructure program. Its purpose is to encourage, through 3-year research contract awards, the development of health-related applications of scalable, network aware, wireless, geographic information systems, and identification technologies in a networked environment. The initiative focuses on situations that require, or will greatly benefit from the application of these technologies in health care, medical decision-making, public health, large-scale health emergencies, health education, etc.

The Library has a program of grant assistance for research, training and fellowships, medical library assistance, improving access to information, and publications. For more than 30 years NLM has supported medical informatics research and the training of medical informaticians at universities across the nation. NLM funding has been instrumental in the development of pioneering electronic health record systems now considered models for the nation and for the training of generations of leaders in the field of informatics. Today the training programs also emphasize opportunities for training in bioinformatics, the field of biomedical computing for the large datasets characteristic of modern research. At present, NLM provides 18 grants to biomedical informatics training at 26 universities, supporting 250 trainees. A new initiative to expand the scope of these training programs is a collaboration between the NLM and the Robert Wood Johnson Foundation that is establishing public health training tracks at several of these sites. In this post 9/11 era the sophisticated use of public health information—whether for timely detection of disease outbreaks or rapid dissemination of information to clinicians and the public in an emergency—is a subject of great importance.

An important contribution of NLM to the infrastructure of medicine is the Unified Medical Language System. This project develops and distributes multi-purpose electronic "Knowledge Sources" and associated lexical programs for system developers. The purpose of these UMLS databases and programs is to help computer systems behave as if they "understand" the meaning of the language of biomedicine and health. The UMLS Metathesaurus, the heart of the UMLS Knowledge Sources, contains more than 1 million concepts and 4.5 million unique concept names from more than 100 different biomedical vocabularies and classifications, including the three principal clinical vocabulary standards: SNOMED CT (Systematized Nomenclature of Medicine–Clinical Terms), LOINC (Logical Observation Identifiers, Names, Codes), and the RxNorm clinical drug vocabulary. NLM has been instrumental in making these standards freely available through U.S.-wide licensing contract support, or direct development.

These resources are especially important to the Federal government's plans to achieve always-current, always-available electronic health records (EHRs) for most Americans within a decade. The lack of common, readily available electronic medical terminology standards has been a major obstacle to the widespread deployment and effective use of EHRs. NLM is playing an important role in remedying this situation with the national licensing of SNOMED CT and its uniform distribution with other clinical and administrative standards within the UMLS. It is now possible for software vendors, health care providers, hospitals, insurance companies, public health departments, medical research facilities, and others to incorporate uniform terminology into their information systems much more readily. This is an important step toward establishing interoperable electronic health records that can be made avail-

able wherever and whenever patients need treatment. In addition to improving the safety and quality of health care, standard electronic health data will assist in detecting and responding to public health emergencies and provide one of the key building blocks for a cost-effective national research infrastructure.

In summary, the National Library of Medicine has a central part to play on today's health care scene. It continues to be a freely accessible archive of the world's published biomedical literature and collection of genomic data, relied on by scientists and health professionals around the world. Millions of people view the Library as a source of trusted consumer health information and access the MedlinePlus and other NLM resources for the public. And the U.S. health care system, as it evolves to take advantage of new information technologies, will rely on infrastructure advances made by the NLM in the area of standard and widely shared terminology.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF ELIZABETH G. NABEL, M.D., DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's Budget request for the National Heart, Lung, and Blood Institute (NHLBI). The fiscal year 2006 budget includes $2,951,270,000, an increase of $10,069,000 over the fiscal year 2005 enacted level of $2,941,201,000 comparable for transfers proposed in the President's request. I come to you with pride on behalf of the NIH component that is responsible for much of the gain in life expectancy that we have enjoyed over the past three decades in the United States, as shown in this chart. At the same time, however, I come with deep concern because the diseases under NHLBI responsibility still comprise three of the four leading causes of death in this country—heart disease, stroke, and chronic obstructive pulmonary disease (COPD). Clearly, we have come a long way, but we have far to go.

A VISION FOR THE FUTURE OF THE NHLBI

As the NHLBI's first new director in 22 years, I would like to take this opportunity to share with the Committee my vision for the Institute. This vision is based upon a fundamental set of values—excellence, integrity, innovation, respect, and compassion—that will permeate all activities in the NHLBI. I believe that scientific discovery provides the basis for progress and that the NHLBI is uniquely positioned to catalyze changes that must be made to transform our new scientific knowledge into tangible benefits for the people of this country. Within this framework, let me articulate four themes that will guide priority setting of our research agenda.

THEME ONE: DISCOVERY

The first theme—stimulating basic discoveries of the causes of diseases—is vital to developing new, critically needed treatments. Basic research provides the foundation of the NHLBI portfolio and has been one of its great strengths. The typical model of investigation—research conducted by single investigators or small groups of investigators on projects of their own inspiration—accounts for most of the unanticipated and major scientific discoveries in this country. I believe strongly that we must protect and nurture investigator-initiated research. The NHLBI will continue to invest in the most talented scientists conducting the highest caliber research. Innovation and creativity using the most advanced biomedical technologies will be our goal.

We have an exciting opportunity to support emerging new scientific fields. Major strides are being made in computer sciences, bioengineering, material sciences, chemistry, and other areas of study that vastly benefit medical research, and the pace of discovery in these disciplines should be accelerated. One approach is to develop funding mechanisms (e.g., for support of high-risk research) that encourage innovative thinkers to turn their attention to the major current challenges in heart, lung, and blood diseases.

Another objective is to generate large, publicly available sets of reagents and data that could function as a "tool kit" for NHLBI investigators. Gene sequences and maps, cell lines, knockouts and knockdowns of genes in selected animals, reference sets of proteins, protein affinity reagents, and libraries of small molecules are examples of resources that will provide our investigators with the technologies required for innovative discoveries.

THEME TWO: TRANSLATION

Our second task is to speed translation to clinical applications so that people can benefit as quickly as possible from the basic research enterprise. Clinical research, and more specifically, translational research ("bench to bedside") are vital to our mission, so that we can translate basic discoveries into the reality of better health for our country.

The NHLBI must further develop the infrastructure for clinical research so that it serves the evolving field of scientific discovery and provides a foundation for evidence-based clinical decision-making. Clinical research is critical to ensuring that new products and techniques are safe and effective before they are widely applied. However, clinical research is often time-consuming and inefficient, and is increasingly burdened by regulatory hurdles. Our challenge is to expand clinical research to complement the exciting basic science discoveries, while making it more efficient and cost-effective.

We intend to develop a translational research agenda supported by clinical trials, clinical networks, and clinical workforce training. Key components will focus on increasing interactions between basic and clinical investigators and easing the movement of new tools from laboratories to clinics. We will build upon our rich experience with clinical trials and networks to develop new partnerships among organized patient communities, community-based physicians, and academic researchers. We will work on improving bioinformatics and clinical databases, standards for clinical research protocols, measures of clinical outcomes, and quality assessment. Translational research requires the expertise of many fields and should include analysis of health education, outcomes, health-care delivery, and health-care economics. This focus fits well with the Re-engineering the Clinical Research Enterprise of the Roadmap.

The NHLBI must cultivate a cadre of clinical researchers who have skills commensurate with the complexity and needs of our research enterprise. Clinicians must be trained to work in the interdisciplinary, team-oriented environments that characterize today's research efforts. We further anticipate that specific training will be required in an array of disciplines important to clinical research, including genetics, epidemiology, biostatistics, and behavioral medicine.

At the core of this vision is the need to develop new partnerships of research with organized patient communities, community-based health care providers, and academic researchers. We will rely on our partnerships to facilitate the conduct of this clinical research, to train our clinical investigators, and most important, to achieve our common goals of improved health for the public.

THEME THREE: INTERACTIONS

The third theme is facilitating communication between scientists and physicians so that new ideas can be generated, shared, and advanced.

Today's science is far more complex than that of yesteryear. Research, whether basic or clinical, is now commonly done by teams of scientists wherein each individual brings specific talents and expertise to the overall effort. We will stimulate and facilitate the conduct of interdisciplinary research, so that advances can be made more quickly. Principal-investigator status will be granted not to just one investigator, as is the norm, but to all key members of the research team. Integrated reviews of grants will take into account the melding of various disciplines to address the problem at hand, and interdisciplinary teams will be encouraged to evolve in both directed and unexpected ways.

An essential component of our efforts in research collaboration will be community-based clinical trials, which enhance the conduct of clinical research at academic medical centers. An outstanding example is our ALLHAT (Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial), in which physicians from many types of medical settings—a total of 623 sites in 47 states, Puerto Rico, the United States Virgin Islands, and Canada—successfully enrolled over 42,000 patients and followed them for 6 years. The physicians participated because they believed in the importance of the scientific questions being addressed with regard to patient care and because of the direct benefits of participation to their patients, including free medications. These community-based physicians conducted the trial at very high standards—follow up was over 97 percent. As part of our plan to disseminate the ALLHAT results, participating community physicians are now working with other doctors in their local communities to treat patients with high blood pressure.

THEME FOUR: COMMUNICATION

Our fourth task is to effectively communicate our research advances to the public to improve understanding of new, promising science.

The NHLBI has an outstanding history of outreach in the areas of high blood pressure, cholesterol, asthma, heart attack, obesity, sleep disorders, and women's cardiovascular health, and new efforts are under way with respect to COPD and peripheral arterial disease. I wholeheartedly support these programs that serve the mission of our Institute and the Nation. Education of our patients and the public regarding prevention and treatment of heart, lung, blood, and sleep disorders is one of my highest priorities.

We will continue to work collaboratively with our colleagues in the DHHS, including the CDC and the FDA, to support prevention and control programs. We also have an unprecedented opportunity to build upon our partnerships with professional organizations, who have a large stake in developing and implementing practice guidelines and monitoring their effectiveness, and with patient advocacy groups. One of our most gratifying partnership programs has been The Heart Truth, which is successfully raising awareness nationwide that heart disease is the leading cause of death among American women. The "reach" of this campaign continues to expand as we forge additional fruitful partnerships with entities in the public and private sectors.

Disparities in health status constitute a significant global issue. Research is essential to understand the diverse contributions of genetics, health behavior, diet, socioeconomic status, culture, and environmental exposures in the genesis of health disparities in heart, lung, and blood diseases and to formulate, evaluate, and disseminate well-conceived, focused intervention programs. This work will necessarily entail a vigorous effort to increase the representation of minorities in the ranks of NHLBI researchers. We are also cognizant of the need to improve and expand programs to prevent, manage, and treat diseases and conditions that disproportionately affect U.S. minority and underserved populations, such as cardiovascular disease and asthma, and to evaluate the effectiveness of our research, treatment, and education programs. A full resolution of the health disparities problem will occur only through committed and sustained efforts by many in our government, health centers, and society.

SUMMMARY

The realization of this vision will require the efforts of many. We are engaged in a special form of public service, that is, the promotion of patient and public health. I will work diligently to preserve public trust in the Institute, the NIH, and the biomedical research enterprise, and to ensure that the NHLBI serves the public with the highest level of integrity. This trust is essential for meeting our common goals of making important new scientific discoveries and translating them to improve health in this country.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. KENNETH OLDEN, DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute of Environmental Health Sciences (NIEHS). The fiscal year 2006 budget includes $647,608,000, an increase of $3,103,000 over the fiscal year 2005 enacted level of $644,505,000 comparable for transfers proposed in the President's request.

INTRODUCTION

"Genetics loads the gun, but environment pulls the trigger."——Judith Stern, University of California, Davis

The Nation needs better information to promulgate evidence-based environmental health regulatory policies and to prevent or cure most chronic diseases. This paucity of information has an enormous impact on the world's economy, both in terms of costs associated with health care and with regulatory compliance. In large measure, this situation exists because we still do not understand what role the environment plays in human health and disease. The application of knowledge and technologies developed through the pursuit of the Human Genome Project offers great promise for elucidating mechanisms of gene-environment interactions in the development of complex diseases.

For years, the environment was considered to have a minor role in the etiology of human illness. But, in recent years, the thinking has shifted in favor of gene-environment interactions. For example, recent studies show that no more than one-third of the cancer burden can be attributed to the action of genes alone (Verkasala, et al., 1999, *Int. J. Cancer* 83:743–749; Lichlenstein, et al., 2000, *NEJM* 343:78–85), only 15 percent of Parkinson's Disease (Tanner et al., 1999, *JAMA*, 281:341–346), and about a third of autoimmune diseases (Powell, et al., 1999, *Env. Health Pers.* 107 (Suppl. 5), 667–672). A more recent study reported that 90 percent of individuals with severe heart disease have at least one or more of four classic risk factors captured in the current definition of the environment (Khat et al., 2003, *JAMA* 290:899–904). Because of these and other findings, it is now generally accepted that more informative, cost-effective, high-throughput methods for assessing and predicting risk resulting from environmental exposures will need to be developed. Otherwise, we will not be able to prevent or cure most chronic diseases, and the costs associated with health care and environmental regulatory compliancy will continue to escalate.

Starting in 1997, NIEHS developed several new research initiatives to respond to this urgent need. Such programs include: the Environmental Genome-Project (Kaiser, 1997, *Science* 278:569–570; Brown and Hartwell, 1998, *Nat. Genet.* 18:91–93), the National Center for Toxicogenomics (Kaiser, 2003, Science 300:563), and the Mouse Sequencing Project (*Nature* 432: 5, 2004). While the results from these three initiatives will provide information relevant to most chronic diseases, other research programs have been developed to address specific diseases such as breast cancer, Parkinson Disease, and autism. Today, I will briefly describe several of these initiatives and their implications for human health and disease.

GENETIC DIFFERENCES IN SUSCEPTIBILITY TO DRUGS AND ENVIRONMENT

Individuals vary, often significantly, in their response to environmental agents. This variability provides a high "background noise" when scientists examine human populations to identify environmental links to disease, often masking important environmental contributors to disease risk. Fortunately, the Human Genome Project created tools that can help identify the genetic variations in environmental response genes that can lead to such wide differences in disease susceptibility. NIEHS developed the Environmental Genome Project (EGP) to catalogue these genetic variants (polymorphisms) and to identify the ones that play a role in human susceptibility to environmental agents. This information is already being used in epidemiological studies to better pinpoint environmental contributors to disease. Also, several important variants have been discovered that are associated with risk for chronic illnesses such as leukemia, cardiovascular disease, and neuronal dysfunction.

ANIMAL MODELS PREDISPOSED TO ENVIRONMENTAL RISK

The usefulness of the susceptibility data generated in the EGP is enhanced by the availability of animal models with the exact sequence variations discovered by re-sequencing of the human environmental response genes. Therefore, NIEHS developed a university-based Mouse Genomics Centers Consortium to create mice with such variations and provide them to the scientific community. To date, approximately 20 well-characterized mouse models have been developed. These models represent a variety of disease endpoints, including: Werner's syndrome (aging disorder), diabetes, mammary cancer, gastrointestinal and bladder cancer, prostate cancer, and skin cancer.

EFFORT TO IMPROVE RELEVANCE OF ANIMAL MODELS

Environmental health scientists often use mice to predict how environmental agents might affect people. Although mouse studies can indicate the potential of an exposure to cause cancer and other diseases, there is no way to precisely extrapolate these study results to the risk in humans. Information on the similarities and differences in homologous genes between human and mouse is important to improve accuracy in predicting human risk. While laboratory mice might look alike, the 100 different strains used in medical research differ significantly in their behavior, physiology and susceptibility to drugs and environmental agents (e.g., carcinogens), and scientists are eager to discover the differences in the genetic sequences that underlie these traits, with the goal of finding counterparts in humans. NIEHS initiated a mouse sequencing project to decipher the genomes of the 15 mouse strains used most frequently in research to predict human risk. Such data will improve environmental risk assessment decisions and will help researchers in choosing the most appropriate strain for studying toxicity.

SISTER STUDY OF BREAST CANCER

A unique study exploring gene-environment interactions in breast cancer development has begun nationwide recruitment. It will look at how genes, activities of daily life, and environmental exposures affect breast cancer risk. To get the information quickly, this study is recruiting 50,000 symptom-free women who have a sister that had breast cancer. These women are at increased risk of breast cancer, share many genes with their affected sibling, and would have experienced many of the same exposures. For these reasons, it is expected that a sufficient number of women will develop breast cancer within 10 years and their genes and exposures can be compared with those of women in the study who did not develop the cancer. A broad range of exposures will be examined, including personal care and household products, workplace exposures, and dietary factors, along with genetic analysis. The principal investigator has the active support of the American Cancer Society, Sisters Network, Inc., the Susan G. Komen Breast Cancer Foundation, and the Y-ME Breast Cancer Organization.

PARKINSON'S DISEASE

A major impediment in Parkinson's Disease (PD) research has been the lack of rapid communication between epidemiologists, laboratory researchers, and clinicians which prevents the type of multidisciplinary approach this field needs. To encourage advances in this important area of study, NIEHS developed a multidisciplinary Collaborative Centers Program for Parkinson's Disease Environmental Research. This multi-institutional approach is designed to accelerate the identification of genetic and environmental factors leading to PD. Collectively, the three centers have expertise in basic neurosciences, human genetics, clinical research, and epidemiology, as well as long-standing interactions with patient groups. Accomplishments to date include: efforts to discover new PD susceptibility genes; development of a registry in California to track the disease; development of mouse models with specific alterations in genes suspected of playing a role in PD, and efforts to develop a primate model of PD that exhibits the most prominent clinical features of the disease.

AUTISM

Autism is a devastating behavioral disorder that most likely arises from underlying genetic susceptibilities interacting with specific environmental exposures during pre- or post-natal development. A number of people have suspected that the mercury-containing compound thimerosal, used to preserve childhood vaccines, could be an environmental trigger for autism development, based on the established neurotoxicity of higher doses of mercury. Extensive epidemiological studies, however, have failed to provide any association between vaccines and autism. It is possible, however, that only a subset of children are susceptible to mercury effects, perhaps when coupled with an immunological challenge. Preliminary animal studies have provided an intriguing clue to possible susceptibilities that NIEHS is now pursuing. In these studies, different mouse strains were exposed to thimerosal at ages and doses that corresponded to the standard protocol for childhood vaccinations. Only the immunologically deficient strain of mouse exhibited a response. In these mice, behavioral effects were reported and morphological changes were observed in the brain. However, this study did not have sufficient power to be definitive. Fortunately, the NIEHS already had two Children's Environmental Health and Disease Prevention Research Centers devoted to autism. Thus, the Institute provided a supplement to one of these Centers to do more extensive testing of thimerosal in autoimmune-prone (SJL) mice. This Center has expertise in evaluating critical social behaviors, as well as the ability to conduct state-of-the-art stereology to measure brain effects such as volume changes and changes in cell number occur. This more extensive look at thimerosal-immune co-contributors to brain damage may provide better insight into this disorder than previous studies have. In addition, the same Center is recruiting a cohort of 700 autistic children, and appropriate control subjects, to further examine the role of gene-environment interactions in the etiology of autism.

OBESITY AND THE BUILT ENVIRONMENT

Obesity is a major contributor to human disease and rising health care costs. NIEHS is collaborating with the Robert Wood Johnson Foundation to examine how community design influences physical activity. This so-called Active Living Design Program is working with local governments to influence city planning and land use decisions. The program's impact on physical activity, obesity, and other health indicators will be assessed. The Institute is also encouraging research to evaluate the role of "in utero," neonatal, and pre-puberty exposures to environmental estrogens

and other compounds in the onset and development of obesity, as well as examining gene-environment interactions that favor weight gain.

NANOTECHNOLOGY

Nanotechnology is an exciting area of research with broad implications for multiple industries, including medicine and communication. For example, nanoscale devices have the potential to deliver therapeutic and imaging agents to specific cells and tissues in ways not presently possible. However, when bulk material is converted to ultrafine nanoparticles, its physical, chemical, and biological properties can be altered in ways that might adversely affect health. So, while many laboratories are focused on exploiting the rich potential of these agents, there is little activity to assess their toxicological properties. NIEHS, under the auspices of the National Toxicology Program (NTP), has initiated a program to evaluate the toxicological properties of the major classes of nanoscale materials and will investigate fundamental questions such as: How are nanoscale materials absorbed, distributed in the body, and taken up by cells? Are there novel toxicological interactions? What are the appropriate detection and quantification methods for nanoscale particles?

NIH ROADMAP AND ENVIRONMENTAL HEALTH RESEARCH

The ability to investigate and understand issues in environmental health requires collaboration between many scientific disciplines: epidemiology, toxicology, molecular biology, clinical sciences, and many others. Thus, Roadmap initiatives such as the Interdisciplinary Research Planning Centers will greatly enhance NIEHS' work. Examples include: the use of geographic/spatial methodologies to address combined genetic, social, and environmental factors on child health and development, and an effort to redefine computational genomics with emphasis on gene-environment interactions in alcoholism, atherosclerosis and breast cancer. Both projects have strong ties to other significant NIEHS-funded programs at the same institutions.

Thank you for the opportunity to comment on the important work supported by the NIEHS. I will be happy to answer any questions you might have.

PREPARED STATEMENT OF DR. JOHN RUFFIN, DIRECTOR, NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Center on Minority Health and Health Disparities (NCMHD). The fiscal year 2006 budget includes $197,379,000, an increase of $1,220,000 over the fiscal year 2005 enacted level of $196,159,000 comparable for transfers proposed in the President's request.

The NCMHD has just entered its fourth year of operation. Much has been accomplished during this time. However, much remains to be done. Racial and ethnic minorities and other health disparity populations continue to suffer a disproportionate burden of illness, disability and premature death. Health disparities cover a broad spectrum of health conditions and diseases that include cancer, mental illness, infectious diseases, autoimmune diseases, endocrine diseases, vascular diseases, infant mortality, diabetes, HIV/AIDS, obesity and nutritional deficiencies. There are many factors that contribute to health disparities such as genes, biology, culture, race, environment, socioeconomics, and health behavior. Due to the interaction of these complex factors, the elimination of health disparities requires a multifaceted approach.

NIH HEALTH DISPARITIES STRATEGIC PLAN

The Congress has charged the NCMHD to lead the Federal effort in health disparities research, research capacity building, and outreach. The NCMHD guides the NIH efforts in collaboration with NIH Director, the other NIH Institutes and Centers, and the NCMHD's Advisory Council in revising the *NIH Health Disparities Strategic Plan* annually. The plan represents the trans-NIH health disparities vision and strategy to eliminate health disparities through research, research infrastructure, capacity building, and community outreach.

The NIH Institutes and Centers (ICs) are committed to educating minority patient populations on disease management and quality care. Several of the ICs plan to increase the number of culturally relevant health educational materials and to develop and expand linkages with minority organizations and professional societies to increase dissemination of research advances to minority-serving institutions, and racial and ethnic minority and health disparity communities. For example, the National Institute of Allergy and Infectious Diseases (NIAID) will produce a series of low-literacy fact sheets on sexually transmitted infections, HIV/AIDS, and tuber-

culosis. The NINDS expanded its health education program, *Know Stroke. Know the Signs. Act in Time.*, to populations at high risk for stroke—African Americans, Hispanics, and seniors—in communities that have the health care systems in place to treat them. The National Center for Complementary and Alternative Medicine (NCCAM) will employ multimedia technology, such as web chats, teleconferences, and minority-focused media to disseminate information about complementary and alternative medicine.

The National Cancer Institute (NCI) is achieving significant progress toward understanding and addressing the needs of the Hawaiian and Pacific Basin populations through a five-year cooperative agreement with Papa Ola Lokahi, a Native Hawaiian owned-and-operated community-based health organization. Through this agreement, the NCI funds a variety of culturally competent cancer awareness, research, and training activities.

The National Heart, Lung and Blood Institute (NHLBI) is initiating a new program to address the substantial and growing burden of Cardiovascular Disease (CVD) in American Indians and Alaska natives. This initiative will develop and test culturally appropriate interventions to promote the adoption of lifestyles and behaviors that are known to reduce biological and CVD risk factors, such as high blood pressure and cholesterol levels, obesity, glucose intolerance, and diabetes.

NCMHD HEALTH DISPARITIES IMPACT

In addition to developing the NIH Strategic Plan, the NCMHD has focused attention on the pressing need to establish its programs. The national reach of the NCMHD extends to more than 100 institutions and more than 500 individuals that have received awards to train for health professions careers, conduct health disparities research, build research capacity and advance outreach efforts.

The NCMHD Health Disparities Centers of Excellence (Project EXPORT) program currently funds seventy-one institutions in 29 states engaged in multidisciplinary research. Priority research focus areas include cancer, cardiovascular disease, stroke, diabetes and the health of mothers and their infants.

Communities nationwide in states such as Alabama, New York, Pittsburgh, Montana and Hawaii are being encouraged and equipped for participation in clinical studies and for partnering in the conduct of evidence-based disease prevention and intervention activities. The Clemson University-Voorhees College Project EXPORT partnership has three studies focused on obesity. Using a network of community-based partners, each study examines diet and/or physical activity levels of rural residents or students. The objectives of the studies are to identify the socio-cultural factors influencing choices and determine how environmental effects and knowledge of nutrition and physical activity impact choices about diet and exercise.

Culturally competent health care is an essential component in defeating health disparities and requires a distinct sense of urgency. In a recent study on cultural competence among physicians treating Mexican Americans who have diabetes, supported by a NCMHD-Center of Excellence, scientists determined that physicians can increase cultural competence and effective care by becoming self-aware of their knowledge, views, and attitudes about cultures and ethnic groups, and by engaging in culture-focused educational activities. Recognizing that culturally appropriate actions can be predicted, based on a provider's awareness that culture is relevant to medical care and that negative preconceptions can hinder the effectiveness of health care delivery, is an important finding for improving cultural competence and reducing health disparities.

The NCMHD Research Endowment Program, unique within the NIH, is best described as inclusive and diverse. Fourteen institutions receive NCMHD endowment funds to enhance research capacity and infrastructure for research and training. The activities of the institutions involve strengthening teaching programs in the biomedical and behavioral sciences; establishing endowed chairs and programs; obtaining state-of-the-art equipment for instruction and research; and enhancing the recruitment and retention of student and faculty from health disparity populations. A NCMHD Endowment Program award to the University of Kansas has enabled the university to develop a K–12 pipeline to recruit students through summer programs; retain and graduate 95 percent of underrepresented minority medical students; increase underrepresented minority faculty members from 24 to 39; and provide opportunities for 48 underrepresented minority students to participate in health disparity research over the summer.

The NCMHD supports two loan repayment programs—the Health Disparities Research Loan Repayment Program (HDR) and the Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (ECR), to promote a diverse and strong scientific workforce by alleviating the financial bar-

riers that often discourage many talented health professionals from health disparity, medically underserved and disadvantaged communities from pursuing a research career.

The NCMHD funds are supporting the deployment of 466 emergent researchers to 42 states and the District of Columbia to conduct health disparities research. These programs are the foundation for developing a lasting relationship with talented and committed health disparities scholars. Fifty-six percent of the awardees in the HDR program are members of a health disparity population. The loan repayment programs exemplify the multidisciplinary approach needed to address health disparities. For example, epidemiology, pharmacology, linguistics, etiology, ethnography, health policy, and behavioral science are among the program's research disciplines. Research includes: identifying barriers to health care access; race and long-term diabetes self management in an HMO; a comparison of androgen receptor for polymorphism in African American and Caucasian women with breast cancer; and reducing HIV/STI risk in young adult minority populations.

The number of participating institutions in the Research Infrastructure in Minority Institutions (RIMI) Program has tripled since 2001. Program accomplishments include faculty seminar series on health disparities research; research on the health and developmental impact of methamphetamine production in New Mexico children, and the establishment of a Natural Toxins Research Center. The NCMHD will continue to build upon the RIMI program by exploring partnerships among tribal colleges, community/junior colleges, and non-research intensive four-year institutions with major research-intensive colleges and universities.

The Minority Health and Health Disparities International Research Training Program (MHIRT) positions the NCMHD in collaboration with the NIH Fogarty International Center, to extend its health disparities research and training capacity across borders. The MHIRT program enables students and faculty from health disparity populations to participate in international research training opportunities in countries such as South Africa, Sweden, Italy, Mexico, Bulgaria, Thailand, Trinidad, China, Australia, Brazil, and Senegal. Research efforts include cancer epidemiology, reproductive biology, parasitology, malaria, ethnopharmacology and neurobiology.

COMMUNITY-BASED PARTICIPATORY RESEARCH AND OUTREACH

The NCMHD recently established an Office of Community-Based Participatory Research and Outreach, and launched a new program that will support collaborative partnerships between academic institutions and community-based organizations for research studies looking at the interface of physical and psychological environments and their health impacts on communities of color and the medically underserved; methodology research looking at effective methods of measuring racism and community level outcomes; evaluation of outcomes; and impact of the research. This program will build on the NCMHD existing community-based research and outreach initiatives through its Project EXPORT program.

FEDERAL RESEARCH COLLABORATIONS

In addition to its core programs, the NCMHD has continued to fund a broad range of collaborations with the other NIH Institutes and Centers, the Department of Health and Human Services, and other Federal agencies. Recently, the NCMHD launched a new initiative to support research relevant to the Mississippi Delta Region and its medically underserved populations. This endeavor involved the collaboration of eight NIH Institutes and Centers with the NCMHD supporting approximately $8 million in research projects.

CONCLUSION

Working with our many research partners, the top priority of the NCMHD is to build a solid and diverse national biomedical research enterprise of individuals, institutions, and communities dedicated to eliminating health disparities. The NCMHD will sustain and expand its primary strategies. Research capacity building will extend beyond academia to involve community and faith-based organizations, individuals, and business at local and grassroots levels. Training and the diversification of the health, scientific, and technological workforce will remain key areas of focus in developing innovative projects. Prevention, treatment, cultural competency, and health care delivery for urban and rural communities will be approached more aggressively. We will continue to strive for an America in which all populations will have an equal opportunity to live long, healthy, and productive lives.

PREPARED STATEMENT OF DR. PAUL SIEVING, DIRECTOR, NATIONAL EYE INSTITUTE

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Eye Institute (NEI). This budget includes $673,491,000, an increase of $4,421,000 over the fiscal year 2005 enacted level of $669,070,000 million comparable for transfers proposed in the President's request. As the Director of the NEI it is my privilege to report on the progress laboratory and clinical scientists are making in combating blindness and visual impairment and about the unique opportunities that exist in the field of vision research.

GLAUCOMA AND OPTIC NEUROPATHIES

Glaucoma is a group of eye disorders that causes optic nerve damage that can lead to severe visual impairment or blindness. Elevated intraocular pressure (IOP) is frequently, but not always, associated with glaucoma. Glaucoma is a major public health problem and published studies find it is the most common cause of visual impairment and blindness in African Americans.

The prevalence of glaucoma is three times higher in African Americans than in non-Hispanic whites.[1] Additionally, the risk of visual impairment is much higher and the age of onset is earlier than in Whites. An NEI-supported follow-up study to the Ocular Hypertension Treatment Study (OHTS) found that early treatment of elevated IOP reduces the risk of developing glaucoma in African Americans. Of the participants in the treatment arm of the study, 8.4 percent developed glaucoma whereas 16.1 percent in the observation group developed the disease. Additionally, the OHTS follow-up study found that certain biological characteristics of the eye including corneal thickness are helpful in predicting who will likely develop glaucoma and who will benefit from therapy. This study provides important treatment and prognostic information for clinicians in caring for this at risk population.

RETINAL DISEASES

Retinal diseases are a diverse set of sight-threatening conditions that include age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinitis pigmentosa, Usher's syndrome, ocular albinism, retinal detachment, uveitis (inflammation) and cancer (choroidal melanoma and retinoblastoma). This year, NEI supported laboratory researchers made great strides in developing therapies for these diseases. For example, a recent NEI study found that eye injections of bone marrow stem cells from adult animals prevented vision loss in two rodent models of retinitis pigmentosa (RP). These findings raise the possibility of a therapy in which patients could receive an injection of their own bone marrow stem cells to preserve vitally important central vision.

Age-related macular degeneration (AMD) is a leading cause of blindness and visual disability in older age Americans. The inability to prevent the development of AMD and its complications is largely due to an imprecise understanding of the pathologic mechanisms of the disease. Genetic and environmental factors have previously been implicated in the disease. A recent NEI supported study in animal models has found evidence that inflammation may also play a role. These animal models suggest that the immune system contributes to the disease and offer new insights into possible mechanisms of the disease. The availability of animal models of the disease will also allow for the testing of new intervention strategies.

CORNEAL DISEASES

The cornea is the transparent tissue at the front of the eye. Corneal disease and injuries are the leading cause of visits to eye care professionals, and are some of the most painful ocular disorders.

The epithelial cells of the cornea form a surface barrier that protects the underlying tissues from the external environment. When this layer is damaged, the epithelial cells normally respond quickly to close the wound and reform the barrier. In some cases, however, this response is defective, leading to the formation of persistent and painful corneal ulcers. Development of more effective treatments for this condition has been hampered by the limited information about the cellular and biochemical events that regulate corneal wound closure. This year, scientists at the NEI discovered that an enzyme called Cdk5 plays a central role in regulating the migration of epithelial cells to close corneal wounds. More importantly they discovered that drugs which inhibit Cdk5 promote cell migration and wound closure.

[1] The Eye Diseases Prevalence Research Group: Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol 122:532–538, 2004.

These findings suggest a new therapeutic approach for treating persistent corneal ulcers and other conditions that impair wound healing. Animal studies are in progress to determine whether inhibitors of Cdk5 can safely be used in the eye to enhance wound healing.

CATARACT

Cataract, an opacity of the lens of the eye, interferes with vision and is the leading cause of blindness in developing countries. It is also a major public health problem in this country. Throughout life, the lens carries out a process of continued growth with epithelial cells dividing and differentiating into fiber cells. As epithelial cells differentiate into fiber cells they become denuded of certain cell components so they will not interfere with vision or cause cataracts. NEI supported scientists have recently discovered that the epithelial cells "borrow" enzymes involved in programmed cell death, or apoptosis, to mediate the destruction of these cell parts. Apoptosis is a normal biologic process that guides an orderly destruction of cells that are no longer functional or needed. This study defines a critical step in how fiber cells are formed and will spark further investigation into whether alterations in apoptotic enzymes play a role in cataract formation.

STRABISMUS, AMBLYOPIA AND VISUAL PROCESSING

Developmental disorders such as strabismus (misalignment of the eyes) and amblyopia (commonly known as "lazy eye") are among the most common eye conditions that affect the vision of children. In addition, published data estimates that more than 3 million Americans suffer from visual processing disorders not correctable by glasses or contact lenses.

It is estimated that 20 percent of preschool children ages 3–4 have a treatable eye condition.[2] While many states are developing guidelines for preschool screening programs, none of the commonly used vision tests have been evaluated in a research-based environment to establish their effectiveness. Initial results from the NEI-sponsored Vision in Preschoolers (VIP) Study found that 11 commonly used screening tests vary widely in identifying children with symptoms of common childhood eye conditions such as amblyopia, strabismus, and significant refractive error. When the best tests are used by highly skilled personnel in a controlled setting, approximately two-thirds of children with one or more of the targeted disorders were identified. These better tests were able to detect 90 percent of children with the most severe visual impairments. The ongoing VIP study will continue to provide state and local agencies with data to select the most effective vision screening exams that are currently available. The VIP study will also help ensure that more children are detected and treated at an early stage when therapy is most effective.

A fundamental issue in neuroscience has been the inability of nerve cells to regenerate. If researchers could develop therapies that overcome this limitation, the deleterious effects of many neurologic diseases and central nervous system (CNS) injuries might be reversed or greatly improved. NEI-supported researchers provoked nerve cell regeneration in rodents by activating a nerve cell's natural growth capacity and using gene therapy to suppress the effects of growth-inhibiting factors. Although vision was not restored, this combined approach stimulated nerve cell regeneration three times greater than prior attempts. Regeneration of the mature CNS would provide an opportunity to treat blindness and other neurologic diseases.

HEALTH DISPARITIES

Census 2000 data indicate that 12.5 percent of residents in the United States, or 35 million people, are Latino. Based on these data, it is estimated that by the year 2025, 61.4 million Latinos will live in this country, making this the fastest growing minority population. However, there is little available data to ascertain the prevalence and severity of major eye diseases in this population. Results from the NEI-sponsored Los Angeles Latino Eye Study (LALES) suggest that Latinos have some of the highest rates of visual impairment and blindness in the United States. The prevalence of visual impairment and blindness in Hispanics increased with age and women were more frequently affected than men. From a socio-economic perspective, Latinos who were unemployed, divorced or widowed, or less educated had increased rates of visual impairment and blindness. The prevalence statistics, coupled with the socio-economic data from LALES concerning the factors that negatively influ-

[2] Comparison of preschool vision screening tests as administered by licensed eye care professionals in the Vision in Preschoolers Study. Ophthalmology 111(4): 637–50, 2004.

ence access to health care, will aid the NEI, through its public education programs, to devise strategies that better target these at-risk populations.

NIH ROADMAP

A major theme of the NIH Roadmap, Re-engineering the Clinical Research Enterprise, is aimed at accelerating and strengthening the clinical research process. This Roadmap theme is consonant with the NEI's own goal of supporting the highest quality clinical research. The NEI and vision research community have anticipated these opportunities by creating networks such as the Pediatric Eye Disease Investigator Group (PEDIG) and the newly launched Diabetic Retinopathy Clinical Research Network. Continuation and expansion of these initiatives should facilitate and hasten the translation of research discoveries from the laboratory to the clinic for the benefit of those afflicted with a range of eye disorders and diseases.

NIH NEUROSCIENCE BLUEPRINT

The NIH Neuroscience Blueprint was launched in 2004 to further enhance cooperation among 15 NIH Institutes and Centers that support research on the nervous system. Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. Among the Blueprint initiatives for fiscal year 2006, NEI will participate in the systematic development of genetically engineered mouse strains for research on the nervous system and training in neuroimaging and computational biology. NEI will also participate with other Institutes in an initiative to provide specialized neuroscience resources such as animal model, imaging, gene sequencing and screening facilities.

Mr. Chairman, this concludes my prepared statement. I would be pleased to respond to any questions you or other members of the committee may have.

PREPARED STATEMENT OF DR. ALLEN M. SPIEGEL, DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) a sum of $1,872,146,000, which includes $150,000,000 for the Special Appropriation for Research on Type 1 Diabetes through Sec. 330B of the Public Health Service Act. The NIDDK transfers some of these funds to other institutes of the NIH and to the Centers for Disease Control and Prevention (CDC). Adjusted for mandatory funds, this is an increase of $8,562,000 over the fiscal year 2005 enacted level of $1,863,584,000 comparable for transfers proposed in the President's request.

I appreciate the opportunity to testify on behalf of the NIDDK. Our Institute supports research to combat a wide range of debilitating chronic health problems, including diabetes and other endocrine and metabolic diseases; digestive diseases; kidney and urologic diseases; blood diseases; and obesity. Through vigorous support of investigator-initiated research and Institute-initiated efforts, the NIDDK will continue to elucidate the fundamental biology underlying health and disease and to explore new strategies for disease diagnosis, treatment, and ultimately, prevention.

FROM THE LABORATORY BENCH TO THE PATIENT'S BEDSIDE

In recent years, ever-advancing technologies have led to an explosion of biomedical knowledge. It is imperative that scientists harness new discoveries to improve medical care. Thus, in addition to supporting critical basic and clinical research, the NIDDK is also bolstering "translational" research, to accelerate the progression of scientific discovery from basic to clinical studies to directly benefit patients. In one stage of translational research, insights gained at the laboratory "bench" spur the design of new strategies for prevention or intervention, which investigators then test in clinical studies—at the patient "bedside." In a second stage of translational research, investigators explore ways to bring successful interventions and lifesaving knowledge from the clinical research setting into the realm of healthcare practice.

With the goal of directing NIDDK translational research investments to enhance efforts on multiple diseases, I established a Trans-NIDDK Translational Research Working Group to identify research obstacles and opportunities. The Working Group charted the progression from basic to clinical research to medical practice for a number of health conditions to identify common themes for future research. These anal-

yses were considered by NIDDK's National Advisory Council; external advice was also received at other scientific meetings.

By way of example, translational research relating to the assessment of blood sugar (glucose) levels has greatly benefited diabetes care. Scientists discovered that levels of a variant of the red blood cell protein hemoglobin, called hemoglobin A1c (HbA1c), correlate with blood sugar levels. In the 1990s, a landmark NIDDK-supported clinical trial demonstrated that people with type 1 diabetes can reduce the risk of eye, kidney, and nerve complications by lowering their HbA1c levels through intensive treatment of blood sugar. As a result of this research, target levels for HbA1c were set, thus improving patient care by encouraging medical practitioners to use a combination of methods to better control blood sugar. This research further led to the FDA's acceptance of the HbA1c level as an end-point sufficiently robust to define clinical benefit in clinical trials. "Biomarkers," such as the level of HbA1c, can facilitate clinical trials and thus stimulate the development of new therapeutic agents. Many new drugs for diabetes have now been FDA-approved based on HbA1c as an outcome.

In another example of successful bench-to-bedside research, NIDDK-supported investigators elucidated the biological defect responsible for the devastating inherited metabolic disease, MPS I; discovered a naturally-occurring dog model for the disease; and tested a potential therapy in dogs. Following clinical testing, this therapeutic agent is now produced by industry and available on the market to treat this disease. These two examples illustrate the critical role of NIH investment in research from bench-to-bedside. Both also spanned several decades from the initial basic research discoveries to clinical application. Thus, a critical goal of NIDDK's new translational research efforts is to accelerate this process.

In one planned translational research effort, the NIDDK will pursue the development of new biomarkers. Examples of diseases or conditions for which such biomarkers would be valuable include acute kidney failure, liver and kidney fibrosis, type 1 diabetes, and insulin resistance—which is associated with type 2 diabetes. The NIDDK will also foster research on biomarkers for interstitial cystitis, including the evaluation of a potential diagnostic marker that emerged from prior NIDDK-funded research.

Among other translational research efforts, the NIDDK will strengthen research to bring new non-invasive imaging techniques from the laboratory to the clinical setting to enhance clinical research on liver, pancreatic, kidney, and urologic diseases. The Institute will also encourage the development of new animal models suitable for preclinical testing of diagnostic, preventive, or therapeutic interventions for diseases within NIDDK's mission. Although a wealth of information about human biology has been and continues to be gleaned from studies of mice and other animals, in many cases existing animal models are insufficient for preclinical testing. Other translational research efforts are capitalizing on fundamental knowledge about how proteins assume their proper structures. This approach, informed by a recent NIDDK-sponsored conference, will help propel the search for therapies for cystic fibrosis and certain liver and kidney diseases, which are caused by defects in protein "folding" or "processing." Translational research promoted by the NIH Roadmap will synergize with these NIDDK efforts to accelerate progress.

Insights gained from clinical observations can open new avenues for basic research studies, which, in turn, will spur new clinical research endeavors. Several NIDDK initiatives are fostering increased collaboration between basic and clinical researchers, including support for ancillary studies to major ongoing NIDDK clinical trials. Such studies will also maximize the Institute's investment in these trials. As part of our new efforts to enhance our research centers programs, the NIDDK will encourage basic and clinical research partnerships to take advantage of the opportunities of research centers.

In addition to the bench-to-bedside research just described, the NIDDK is pursuing strategies to best translate successful clinical research results from patient study volunteers to the public. These efforts include, for example, translating the results of the Diabetes Prevention Program (DPP) clinical trial, which demonstrated that people at high risk for type 2 diabetes can dramatically reduce risk of disease onset through modest weight loss and exercise. To promote these positive findings, the NIDDK launched its campaign, "Small Steps. Big Rewards. Prevent Type 2 Diabetes," with tailored messages and materials developed for ethnic groups at high risk for type 2 diabetes, older adults, and a general audience. In parallel, the Institute is supporting research demonstration and dissemination projects to explore new strategies for effectively translating the DPP results, from clinical trial to community. This research includes testing programs that target different age groups and minority populations.

New translation efforts to combat kidney disease are building upon the recent finding that even modestly-impaired kidney function increases risk of cardiovascular disease and premature death. Avoiding these devastating outcomes requires early awareness of kidney disease and appropriate treatment. Critically important is detection of deterioration in the kidneys' filtering capacity, the glomerular filtration rate (GFR). While GFR is difficult to measure directly, it can be estimated from routinely measured serum creatinine. The NIDDK's National Kidney Disease Education Program (NKDEP) is thus encouraging laboratories that measure serum creatinine to provide clinicians with GFR values. The NKDEP recently launched an education campaign emphasizing the importance of early detection and treatment, and targeting this message to primary care providers and those at high risk for kidney disease.

EXAMPLES OF BASIC AND CLINICAL RESEARCH ENHANCEMENTS

Underscoring a growing health crisis among our Nation's children, this past year an NIDDK-supported pilot study of middle school students uncovered high levels of the "metabolic syndrome," which is a cluster of health problems associated with obesity and increased risk for diabetes and cardiovascular disease. To address the health threats posed by obesity, we developed and published a Strategic Plan for NIH Obesity Research. Informed by extensive input from scientific and lay experts, the Strategic Plan was developed by the NIH Obesity Research Task Force. Since its inception by the NIH Director, I have had the privilege of co-chairing the Task Force with the NHLBI Director, with the aims of synergizing and accelerating obesity research across the NIH. Consistent with the goals of the Strategic Plan, the NIDDK is pursuing a multifaceted obesity research agenda, from basic molecular investigations to novel intervention studies to translational research. For example, the NIDDK is spearheading a new trans-NIH initiative to study how factors such as maternal weight during pregnancy can lead to obesity in offspring. This research has important implications for public health.

In the area of digestive diseases, the *Action Plan for Liver Disease Research* has now been published. It was developed through NIDDK-led efforts with broad external input from the research, professional, and patient-advocacy communities. Examples of the many areas addressed by the Action Plan include developing or improving therapies for hepatitis C; developing tools for early liver cancer detection; and research on living donor liver transplantation. The Action Plan will direct new liver disease research; the NIDDK will also continue major ongoing clinical studies on hepatitis C; biliary atresia, a disease that strikes children; and non-alcoholic steatohepatitis, a fatty liver disease.

The *Action Plan for Liver Disease Research* is part of a larger planning process for research on digestive diseases, which have an enormous burden on the U.S. population. For inflammatory bowel disease, external advice received in previous planning efforts will continue to inform the NIDDK research agenda. New planning efforts will aim to strengthen research on irritable bowel syndrome and other functional gastrointestinal disorders, which are debilitating and highly prevalent but not well understood. Following focused planning efforts relevant to gastroparesis, the NIDDK will establish a new clinical research consortium to study this debilitating syndrome of nausea, vomiting, bloating, and other symptoms which complicates diabetes and other diseases.

In the areas of kidney and urologic diseases, in addition to the efforts described earlier, the NIDDK will encourage partnerships to pursue promising new therapies for polycystic kidney disease, and will launch a new clinical intervention study of children with vesicoureteral reflux, a bladder condition which can impair kidney function.

I have highlighted today examples of NIDDK's many and diverse research plans and efforts. These reflect our strong commitment to improving human health.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. STEPHEN E. STRAUS, DIRECTOR, NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2006 President's budget request for the National Center for Complementary and Alternative Medicine (NCCAM). The fiscal year 2006 budget includes $122,692,000, an increase of $587,000 over the fiscal year 2005 enacted level of $122,105,000 comparable for transfers proposed in the President's request.

In 2004 NCCAM celebrated its first 5 years by reflecting on its contributions to the science of complementary and alternative medicine (CAM) and crafting a second strategic plan that articulates the Center's plans for 2005–2009. The plan is a collaborative effort that was developed with extensive input solicited from the public, CAM practitioners, and experienced scientific investigators; it articulates NCCAM's agenda for researching CAM healing practices, training CAM researchers, and conducting outreach.

It is noteworthy that an independent analysis released in January 2005 of the major scientific and policy issues surrounding CAM use, which was undertaken by conventional and CAM investigators for the Institute of Medicine (IOM) of the National Academies, identified many of the same research and training priorities as had NCCAM in its strategic planning process. The IOM report emphasized that evidence-based science must inform all health care practices, both conventional and CAM.

In accord with the philosophy articulated by the IOM, scientific rigor has been and will remain the foundation upon which NCCAM advances its research agenda. In its first 5 years, NCCAM funded more than 1,200 projects at some 260 CAM and conventional research institutions. The results of these projects are being published in leading medical journals, affording the public and their health care providers better data on which to base decisions on CAM use. The following are a few highlights of NCCAM's recent scientific advances, ongoing activities, and plans that illustrate the Center's progress and future directions.

UNDERSTANDING WHO USES CAM AND WHY

Understanding who uses CAM and why they do so informs NCCAM's research goals, initiatives, and collaborations. In 2004, NCCAM reported results based on survey data collected in partnership with the Centers for Disease Control and Prevention from more than 31,000 Americans. The data revealed that 62 percent of survey respondents used CAM in 2002. Back pain was the single most common reason respondents used CAM, followed by respiratory infections. To track trends in CAM use, NCCAM and the CDC have agreed to undertake a followup survey in 2007. Additional NCCAM-funded survey analyses are also under way to examine in greater detail CAM use in diverse minority populations.

DETERMINING THE EFFECTS OF ACUPUNCTURE

Acupuncture is among the top ten most popular CAM practices in the United States. In spite of its venerable traditions as a therapeutic practice in Asia, scientific research on acupuncture and how it might work is a relatively recent phenomenon. The recent report on the efficacy of acupuncture for osteoarthritis demonstrates the power and promise of the research strategies developed and implemented by NCCAM.

More than 20 million Americans have osteoarthritis, a frequent cause of pain and disability among aging adults. In 2004, NCCAM-funded investigators, building on the results of previous smaller studies, reported the results of the largest randomized, controlled Phase III clinical trial of acupuncture ever conducted. This study of 570 patients demonstrates that acupuncture is an effective complement to conventional treatments in patients with osteoarthritis of the knee.

EXPLORING MIND-BODY MEDICINE

Recognizing the important role of social and behavioral factors in illness and health, NCCAM's new strategic plan describes further growth in the Center's investments on mind-body medicine for a range of diseases. One such study already under way is a clinical trial examining the use of meditation to achieve weight loss and enhance overall health and well-being among obese men and women. Also, in 2004 NCCAM funded a mind-body center as part of its research centers program.

To further stimulate the field of mind-body medicine research, NCCAM is co-funding an initiative with the NIH Office of Behavioral and Social Sciences Research to encourage interdisciplinary collaborations to elucidate processes underlying mind-body interactions and health and to develop health promotion and disease prevention and treatment interventions.

INVESTIGATING DIETARY SUPPLEMENTS AND FOODS

As reported in the NCCAM/CDC survey, herbal products are among the most popular CAM therapies. Although many believe these products to be safe because they are "natural" or have been used for centuries, few of these products have undergone sufficient study of their safety and effectiveness. Research on botanicals is a priority

area, and NCCAM funds numerous studies ranging from basic laboratory investigations to large Phase III clinical trials, to gather data on the nature, safety, and efficacy of popular herbal remedies.

For example, NCCAM supports several interrelated studies of cranberries for preventing urinary tract infections (UTIs), which afflicts approximately 25 percent of women at least once in their lifetime. These include Phase II clinical trials to identify the optimal cranberry formulation, dose, and treatment duration in studies on UTI prevention as well as other smaller studies on the basic mechanisms, pharmacokinetics, and renal clearance of cranberry's major chemical components.

Another priority for NCCAM's dietary supplement research portfolio is chronic liver disease, which claimed the lives of more than 20,000 Americans in 2002 and disproportionately affects minorities. Through the Small Business and Innovative Research program, NCCAM supports development of a standardized milk thistle product, the most promising CAM therapy for liver disease. In collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases, NCCAM will undertake early phase studies of safety and tolerability of milk thistle to determine if a Phase III trial is likely to be successful, and if so, the optimal research design for its implementation.

NCCAM grantees are also examining the potential therapeutic properties of foods such as soy—especially as it relates to alleviating menopausal symptoms and promoting bone health. Last year NCCAM-supported scientists reported that in a study of pain induced by bone cancer, soy-fed mice experienced less pain than those in a control group. A better understanding of how dietary constituents and plant-based nutrients moderate pain may yield further treatments to help patients with chronic pain.

Benefiting NCCAM's botanical research agenda is its partnership with the NIH Office of Dietary Supplements (ODS). This year NCCAM and ODS have renewed their partnership in funding Botanical Research Centers to promote interdisciplinary collaborative studies on dietary supplements.

MEETING THE DIVERSE NEEDS OF SELECTED POPULATIONS

NCCAM has a broad-based research portfolio, reflecting the diversity of individuals who use CAM for help in managing an array of diseases and conditions. For example, understanding how racial and ethnic minorities use CAM is a focus of the Center's research agenda in health disparities. Initiatives are under way to examine the interplay of race, ethnicity, age, gender, and locale to understand how they affect minorities' use of CAM to manage chronic illnesses such as diabetes or asthma. Examining these practices will help direct future research to answer why specific populations use certain CAM practices—for cultural reasons, because of access issues, for economic reasons, or for effectiveness—which in turn will help health care providers better meet the needs of these groups.

Diseases and conditions predominately affecting the elderly are major targets of ongoing investments. For example, NCCAM is supporting the largest randomized Phase III clinical trial to date of Ginkgo biloba to prevent dementia in the elderly. Cardiovascular disease (CVD), the leading cause of death in the United States, is also a research priority for NCCAM. Investigations are ongoing of the ability of green and black tea extracts (Camellia sinensis) to reduce cholesterol absorption and biosynthesis in postmenopausal women and patients at high risk for CVD.

In 2004, NCCAM grantees reported results from a clinical trial in children affected with upper respiratory infections (URI). In the trial, over 400 healthy 2- to 11-year-olds received a placebo or an echinacea product, an herbal identified by the NCCAM/CDC survey as widely used, to determine objectively whether it would reduce the severity of URIs over the 4-month study period. The researchers observed no differences between the two groups in the duration, severity, number of days with fever, and rate of adverse events except for an increased incidence of rashes in children receiving echinacea. Given the widespread use of this product, NCCAM is following up on this research, focusing on prevention of infection, which is how echinacea is usually taken, and studying the mechanisms by which echinacea may have health effects.

In the wake of the Women's Health Initiative, NCCAM is developing a diverse research portfolio to explore use of CAM in treating menopausal symptoms, including hot flashes and osteoporosis. Some studies are examining the safety and efficacy of a range of CAM modalities women now use to treat these symptoms; others address more basic science questions, such as a therapy's mechanism of action. NCCAM's research portfolio also addresses other important health conditions exclusive to women—endometriosis and premenstrual syndrome (PMS)—as well as those that af-

fect more women than men, such as UTIs, osteoporosis, fibromyalgia, osteoarthritis, breast and other cancers, and cardiovascular disease.

PARTICIPATING IN TRANS-NIH INITIATIVES

NCCAM co-chairs a critical component of the NIH Roadmap for Medical Research Activity, Reengineering the Clinical Research Enterprise, to develop a more effective and cost-efficient model of translational research to move basic research into safe, well-designed clinical trials. In addition, NCCAM is actively involved in the NIH Neurosciences Blueprint, a trans-NIH initiative to accelerate the efficiency and pace of neurosciences research. Also, as part of the Trans-NIH Obesity Initiative, NCCAM is co-sponsoring efforts on childhood obesity and obesity prevention and treatment.

CHARTING NCCAM'S FUTURE

NCCAM has accomplished much in its first 5 years. The first NCCAM-supported large-scale clinical trials are nearing completion; these findings are appearing in the nation's leading medical journals. NCCAM also has developed a comprehensive communications program to inform the public and health care professionals about CAM research findings. And the Center has created new opportunities in CAM research training for young scientists and has forged linkages between CAM institutions and conventional research centers. With its second strategic plan as a guide, NCCAM looks forward to making ongoing contributions as the nation's lead CAM research agency.

Thank you Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. LAWRENCE A. TABAK, DIRECTOR, NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Dental and Craniofacial Research (NIDCR) for fiscal year 2006. The fiscal year 2006 budget includes $393,269,000, an increase of $1,440,000 over the fiscal year 2005 level of $391,829,000 comparable for transfers proposed in the President's Request.

THE ROAD AHEAD: MERGING SCIENTIFIC VISION AND TECHNOLOGY DEVELOPMENT

Many of the opportunities that now face our nation's oral health researchers have never been more exciting or scientifically challenging. For the first time, we can envision a day when early stage tooth decay will be reversible with remineralizing solutions that patch the tooth and halt the disease process before a filling is required. Researchers will soon begin to learn how to engineer teeth and their constituent parts in the laboratory and transplant them into the mouth to replace a missing tooth or damaged tissue. The day also is approaching when saliva will be a reliable diagnostic fluid to detect systemic diseases, providing a rapid, non-invasive alternative to blood-based tests. These are but a few of the many opportunities that await us. And yet, as important as these visions of the future are in setting the course toward improved public health, it is abundantly clear that the road ahead will be blocked unless we develop new tools and technologies for working within the complex microenvironments of the human body. It is this merging of scientific vision with technology development that the NIDCR is fostering within our nation's oral research community and which I would like to highlight.

EARLY DIAGNOSIS TO PREVENT DENTAL CARIES

Let me begin with one of the examples just mentioned. Despite dramatic reductions in tooth decay in the United States over the last half century, dental caries remains a significant public health problem, particularly among disadvantaged population groups. Dental decay also is an unexpected impediment to timely deployment of military personnel. At a time when our nation remains at war, dental readiness has been cited in testimony by the Reserve Officers Association as the number one deployment problem for National Guard and Reserve members. In a 2002 Department of Defense study, 34 percent of military personnel required dental care before they could be deployed, compared to only 16 percent in 1998.

The NIDCR will soon launch an initiative to evaluate the ability of emerging technologies to accurately and reproducibly measure extremely subtle changes in dental enamel that signal the earliest phases of dental caries. While this initiative may sound highly technical, its outcome could play an essential role in transforming den-

tal care. Treatments with the potential to remineralize tooth surfaces in the very earliest stages of decay, long before a filling is needed, are emerging. In anticipation of the required clinical trials to rigorously evaluate these treatments, NIDCR will soon launch an initiative to ensure that microscopic changes in a tooth's mineral content can be measured accurately and reproducibly. Through this enabling research, the evaluation of these treatments will be firmly grounded in science, ensuring the greatest possible benefit to the public.

BIOENGINEERING: BUILDING A TOOTH

Tooth loss has been a public health problem in the United States since the days of George Washington and Thomas Jefferson. Despite revolutionary advances in oral health over the last half century, tooth loss remains a problem, particularly among disadvantaged groups. In addition, tooth agenesis—the lack of one or more permanent teeth—is the most common congenital malformation in humans. While dental implants or dentures are often effective replacements, science has progressed to the point that it may be possible to generate replacement teeth from scratch, which would mark a truly historic advance in oral healthcare and in our understanding of human biology.

Whereas just a few years ago tooth regeneration was far beyond the reach of science, which is no longer the case. An historic opportunity now awaits dental science to learn to seed and reproducibly control the complex, tightly orchestrated cellular and molecular interactions involved in producing a tooth and its supporting structures. The crucial first steps will be to: identify existing gaps in our knowledge of tooth formation; pursue viable solutions from throughout the biological and physical sciences to bridge these gaps; and, based on these comprehensive analyses, formulate blueprints for a complete tooth. Relying on the best of these blueprints, interdisciplinary teams of scientists will begin the process of engineering replacement teeth. It is likely that these investigations will initially yield viable replacement parts, such as enamel, dentin or periodontal ligament, but the ultimate goal is complete tooth regeneration.

LAB ON A CHIP: SALIVARY DIAGNOSTICS

Another particularly exciting area of research is salivary diagnostics. Scientists have long recognized that our saliva serves as a "mirror" of the body's health, in that it contains the full repertoire of proteins, hormones, antibodies, and other molecular substances that are frequently measured in standard blood tests to monitor health and disease. Saliva is easy to collect and poses none of the risks, fears, or "invasiveness" of blood tests. The problem has been that the needed technologies have not existed to adequately develop salivary diagnostics on a large scale.

The Institute continues to support a major research effort that will further develop these needed technologies and create the first comprehensive baseline catalogue of all proteins found normally in oral fluids. This is the initial step in building the needed scientific infrastructure required to expand salivary diagnostics. Already, scientists have begun to evaluate which of the myriad gene products in saliva correlate with various disease processes.

The NIDCR envisions that this basic research could one day translate into miniature, hi-tech tests, or so-called "labs" on a silicon chip, which rapidly scan oral fluids for the presence or absence of multiple proteins linked to various systemic diseases and conditions. Given the ease of sample collection and the breadth of protein markers that could be arrayed on the silicon chip, salivary tests have the potential to revolutionize how diseases are diagnosed. Physicians and dentists would continue to diagnose diseases. But they would be in the position for the first time to monitor a patient's health, producing a comprehensive molecular print out of that individual's health status that can be assessed over time.

Salivary diagnostics will have benefits far beyond medicine and dentistry as well. Law enforcement agencies could employ saliva tests in the field to determine rapidly whether a person is intoxicated or has recently used illegal drugs. These tests may also be beneficial in determining exposures to environmental, occupational, and biological substances, such as anthrax.

ORAL CANCER: EARLY DETECTION IS KEY TO SAVING LIVES

The field of salivary diagnostics recently yielded exciting early findings related to oral cancer detection. According to the American Cancer Society and the Centers for Disease Control and Prevention, oral cancer is the seventh most common cancer among U.S. males and ranks fourth among African American men. Unfortunately, survival rates have not improved significantly in decades. A patient's chance of survival is improved significantly with early detection and treatment. A team of

NIDCR-supported scientists at the University of California at Los Angeles recently reported that they could measure elevated levels of four distinct cancer-associated molecules in saliva and distinguish within 91 percent accuracy between healthy people and those diagnosed with oral squamous cell carcinoma. This "proof-of-principle" study marks the first report in the scientific literature that distinct patterns of "messenger RNA" are not only measurable in saliva, but can indicate a developing tumor. These initial results highlight the potential clinical value of saliva and hold out exciting possibilities for development of commercially available tests capable of delivering early, reliable, non-invasive detection of developing tumors.

PAIN: TRANSLATING TARGETS INTO TREATMENTS

Sizeable gaps exist in our understanding of some of the most basic cells involved in the pain process. Prime examples are the glial cells. For decades, scientists assumed that glial cells primarily played a supportive role in the central nervous system and had no direct influence on the transmission of sensory signals to the brain. But, as more powerful analytical molecular tools have emerged in recent years, scientists now realize that glial cells play a far more important role in pain than was previously appreciated. With this new awareness, it becomes imperative to better define the biology of these cells and their roles in regulating certain aspects of nervous system function.

The NIDCR will launch an initiative that will stimulate needed research into the basic biology of glial cells and their interactions with neurons in causing orofacial pain disorders, such as temporomandibular joint disorders. The initiative will encourage multidisciplinary studies in a variety of areas to define more broadly than ever important aspects of the pain process. Based on this broad investigative approach, key aspects of the pain process will be more clearly defined, pointing the way to unique and highly specific molecular targets for drug development. Without identifying these additional targets, it will be impossible to ever adequately control or treat pain, particularly among the estimated 10 percent of Americans who suffer from chronic pain.

NIH ROADMAP

The NIH Roadmap themes are synergistic with NIDCR research initiatives and provide added impetus to the efforts of oral health researchers. For example, the theme *Re-engineering the Clinical Research Enterprise* is particularly relevant to the development of NIDCR-sponsored dental Practice Based Research Networks. Similarly, the goals of the initiative *Building Blocks, Biological Pathways and Networks* are closely linked to NIDCR's own bioengineering initiative, "Building a Tooth." *Research Teams of the Future* provides an opportunity to further integrate dentists into the new clinical research structure, and highlights NIDCR's longstanding efforts to encourage multi- and interdisciplinary approaches to research questions.

With the above-mentioned examples and other research progress, such as in salivary gene transfer, defining the oral biofilm, and the molecular targeting of oral cancer, NIDCR has never faced more exciting opportunities. By merging our vision of the future with technology development, the road ahead will lead this nation to a new generation of progress and improved oral health.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. JACK WHITESCARVER, DIRECTOR, OFFICE OF AIDS RESEARCH

Mr. Chairman and Members of the Committee, I am pleased to present the fiscal year 2006 President's budget request for the NIH AIDS research programs, a sum of $2,932,992,000, which is an increase of $12,441,000 above the comparable fiscal year 2005 appropriation.

WORLDWIDE PANDEMIC

AIDS is the deadliest pandemic of modern times. More than 20 million people have already died of AIDS, and more than 60 million people around the world have been infected with HIV. AIDS is the leading infectious cause of death worldwide, surpassing tuberculosis and malaria.[1] Its impact is profound, affecting families,

[1] Report on the Global HIV/AIDS Epidemic: July 2002, (UNAIDS/WHO, Geneva, Switzerland, 2002).

communities, agriculture, business, healthcare, education, military preparedness, and economic growth. The United Nations General Assembly's Declaration of Commitment on HIV/AIDS states . . ." the global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and one of the most formidable challenges to human life and dignity, as well as to the effective enjoyment of human rights, which undermines social and economic development throughout the world and affects all levels of society—national, community, family, and individual."[2] According to a U.N. report, "The misery and devastation already caused by HIV/AIDS is enormous, but it is likely that the future impact will be even greater . . . The HIV/AIDS epidemic has erased decades of progress in combating mortality and has seriously compromised the living conditions of current and future generations."[3] A CIA report estimated that by 2010, five countries of strategic importance to the United States—Nigeria, Ethiopia, Russia, India, and China—collectively will have the largest number of HIV/AIDS cases on earth.[4] *Foreign Affairs* magazine stated: ". . . HIV/AIDS is set to be a factor in the very balance of power within Eurasia—and thus in the relationship between Eurasian states and the rest of the world."[5] Dramatic increases in HIV infection also are occurring in Eastern Europe, Central Asia, Latin America, and the Caribbean.

THE U.S. EPIDEMIC

In the United States, according to CDC, the decline in death rates observed in the late 1990s, due largely to expanded use of new antiretroviral therapies (ART), has now leveled off. The use of ART has now been associated with a serious side effects and long-term complications that may have a negative impact on mortality rates. HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age.[6] This means that the overall epidemic is continuing to expand.[7] [8] [9] CDC reports that approximately one quarter of the HIV-infected population in the United States also is infected with hepatitis C virus (HCV). HIV/HCV co-infection is found in 50 to 90 percent of injecting drug users (IDUs). HCV progresses more rapidly to liver damage in HIV-infected persons and may also impact the course and management of HIV infection, as HIV may change the natural history and treatment of HCV.[10]

For the past several years, we have cautioned in our testimony that the appearance of multi-drug resistant strains of HIV presents an additional serious public health concern.[11] [12] [13] [14] [15] In just the past few weeks, we have had a new warning about that potential. The New York City Health Department reported the possibility of a more virulent and aggressive multi-drug resistant HIV strain[16] focusing attention again upon the nature of the infection, the associated immune decline, and the behaviors linked to HIV transmission. It is too early to determine if this is some newly virulent form of HIV. A series of highly sophisticated tests is now underway to examine how the virus replicates in cells, as well as the efficiency and mechanisms of viral attack. The fact that the individual infected by this virus progressed more rapidly to immune decline may be reflective of a number of factors, some unrelated to the viral strain, such as host factors, native immune system function, or genetics. We have much more to learn about this case. However, it highlights a number of lessons about the active and ongoing U.S. HIV epidemic. HIV infection

---

[2] The Impact of AIDS (Department of Economic and Social Affairs, United Nations, 2004).
[3] The Impact of AIDS (Department of Economic and Social Affairs, United Nations, 2003).
[4] Intelligence Community Assessment: The Next Wave of HIV/AIDS: Nigeria, Ethiopia, Russia, India, and China. (CIA, 2002).
[5] The Future of AIDS, Foreign Affairs, November/December 2002.
[6] Characteristics of Persons Living with AIDS and HIV, 2001, HIV/AIDS Surveillance Supplemental Report (CDC, 2003).
[7] Year-End HIV/AIDS Surveillance Report for 2002 (CDC, 2003).
[8] Centers for Disease Control and Prevention HIV Prevention Strategic Plan Through 2005, (CDC, 2001).
[9] Cases of HIV Infection and AIDS in the United States 2003, HIV/AIDS Surveillance Report (CDC, 2004).
[10] Frequently Asked Questions and Answers about Co infection with HIV and Hepatitis C Virus (CDC, 2002).
[11] N. Loder, Nature 407, 120 (2000).
[12] H. Salomon et al., AIDS 14, 17 (2000).
[13] Y.K. Chow et al., Nature 361, 650 (1993).
[14] M. Waldholz, Drug Resistant HIV Becomes More Widespread, Wall Street Journal, 2/5/99.
[15] World Health Report on Infectious Diseases: Overcoming Antimicrobial Resistance, (WHO, Geneva, 2000).
[16] "New York City Resident Diagnosed with Rare Strain of Multi-Drug Resistant HIV that Rapidly Progresses to AIDS," New York City Health Department Press Release 2/11/2005.

does not occur in a vacuum or in isolation—it occurs in the context of behaviors, including alcohol and drug use (the use of crystal methamphetamine in the New York City case), that require a contextually appropriate and interwoven response. This case underscores the importance of access to quality care that may need to include HIV resistance testing, and closer monitoring for immune decompensation in the setting of appropriate treatment. Most importantly, this case is a wake-up call, a reminder that the ability to interrupt HIV transmission, as well as the cycle of pain and suffering associated with HIV disease, is directly related to the robustness of HIV care, treatment and research infrastructure in the communities impacted by this disease. This expanding and evolving U.S. epidemic continues to present new and complex scientific challenges.

ROADMAP FOR NIH AIDS RESEARCH

In response to this worldwide crisis, NIH is the world's leader in the magnitude and quality of our AIDS research effort—a comprehensive program of basic, clinical, and behavioral research on HIV infection, its associated co-infections, opportunistic infections, malignancies, and other complications. No other disease so thoroughly transcends every area of clinical medicine and scientific investigation, crossing the boundaries of nearly all of the NIH Institutes and Centers. The Office of AIDS Research (OAR) plays a unique role at the NIH, establishing a roadmap for the AIDS research program. OAR coordinates the scientific, budgetary, and policy elements of the NIH AIDS program, prepares an annual comprehensive trans-NIH strategic plan and budget for all NIH-sponsored AIDS research; facilitates NIH involvement in international AIDS research activities; and identifies and facilitates multi-institute participation in priority areas of research. These legislative authorities are critical to identify and ensure support for the areas of highest scientific priority.

COMPREHENSIVE AIDS RESEARCH PLAN AND BUDGET

The OAR planning process is inclusive and collaborative, involving the NIH Institutes, eminent non-government experts from academia, industry, foundations, and AIDS community representatives. The Plan serves as the framework for developing the annual AIDS research budget for each Institute and Center, for determining the use of AIDS-designated dollars, and for tracking and monitoring those expenditures. The planning process also serves to monitor and assess scientific progress. The Plan establishes the NIH AIDS scientific agenda in the areas of: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science; Microbicides; Racial and Ethnic Minorities; Women and Girls; Prevention Science; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination.

In consultation with the Director of NIH, the OAR determines the total annual AIDS research budget. The Institutes and Centers submit their AIDS budget request to OAR, and the OAR establishes their AIDS research budgets, in accordance with the priorities of the Plan, at each step of the budget development process.

FUNDING FOR HIGHEST PRIORITY RESEARCH

To develop the fiscal year 2006 request, OAR initiated a comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds to ensure that these projects represent the highest scientific priorities and opportunities. OAR carefully reviewed the mix of investments in key priority areas of research in view of the current epidemic. This budget request reflects OAR's redirecting of AIDS funds to the highest priority projects and new scientific opportunities in fiscal year 2006.

This budget request places highest priority on the discovery, development, and testing of additional HIV vaccine candidates, including funding to move promising vaccine candidates into large-scale clinical trials to evaluate the potential for efficacy. The NIH priority in AIDS vaccine research to date has resulted in approximately 70 clinical trials of nearly 40 vaccine candidates. The evaluation of an AIDS vaccine will require extensive testing in the United States and in international settings where there is a high incidence of HIV.

In the area of therapeutics research, current drug regimens have resulted in extended survival and improved quality of life for many HIV-infected individuals in the United States and Western Europe. However, a growing proportion of patients receiving therapy are demonstrating treatment failure, experiencing serious drug toxicities and side effects, and developing drug resistance. The increasing incidence of metabolic disorders, cardiovascular complications, major organ dysfunction, and physical changes associated with current antiretroviral drugs underscores the critical need for new and better treatment regimens. Improved regimens also are need-

ed to treat HIV co-infections such as hepatitis B and C, as well as other opportunistic infections to reduce drug interactions and problems with adherence to complicated treatment regimens. The goal of this research is to develop new, safe, less toxic, less expensive, and more effective therapeutic agents and regimens.

OAR spearheaded a multi-IC inter-disciplinary collaboration to formalize plans for the restructuring of the NIH clinical trials networks for HIV therapeutics, vaccines and prevention. This effort resulted in a set of principles to guide the development of the Request for Applications (RFAs) for the re-competition of these essential multi-IC supported clinical programs in fiscal year 2006, designed to ensure that they operate effectively and cooperatively, making the best use of research dollars.

Our prevention research priorities include the development of vaccines, topical microbicides, strategies to prevent mother-to-child transmission, including a better understanding of risk associated with breast-feeding, management of sexually transmitted diseases (STDs), and behavioral research strategies, including interventions related to drug and alcohol use. Efforts continue to identify the most appropriate intervention strategies for different populations and sub-epidemics in the United States and around the world.

INTERNATIONAL AIDS RESEARCH

NIH bears a unique responsibility to address the global epidemic, with priority on the urgent need for more affordable and sustainable prevention and treatment approaches that can be implemented in resource-limited nations. The high incidence of Hepatitis B and C, malaria, and TB in many of these nations further complicates the treatment and clinical management of HIV-infected individuals. NIH international AIDS research includes: development of HIV vaccine candidates and chemical and physical barrier methods, such as microbicides; behavioral strategies; strategies to prevent mother-to-child transmission; therapeutics for HIV-related co-infections and other conditions; and approaches to using ART in resource-poor settings. NIH supports international training programs and initiatives that help build research infrastructure and laboratory capacity.

WOMEN AND MINORITIES

In the United States, the rate of diagnoses for African Americans was almost 10 times the rate for whites and almost 3 times the rate for Hispanics. The rate of AIDS diagnoses for African American women was 25 times the rate for white women.[17] Women experience HIV/AIDS differently than men. NIH research has demonstrated that women progress to AIDS at lower viral load levels and higher CD4 counts than men. Women also experience different clinical manifestations and complications of HIV disease. These findings may have implications for care and treatment of HIV-infected women, particularly with ART. NIH is exploring research questions about specific characteristics of women and girls that might play a role in transmission, acquisition, or resistance to HIV infection during different stages of the life course.

We are focusing on the need for comprehensive strategies to decrease HIV transmission in affected vulnerable populations, and improve treatment options and treatment outcomes, including interventions that address the co-occurrence of other STDs, hepatitis, drug abuse, and mental illness; and interventions that consider the role of culture, family, and other social factors in the transmission and prevention of these disorders in minority communities. NIH continues to make significant investments to improve research infrastructure and training opportunities for minorities and will continue to ensure the participation of minorities in AIDS clinical trials, as well as in natural history, epidemiologic, and prevention studies.

SUMMARY

The NIH's leadership role in the response to the AIDS pandemic is fundamental and unprecedented, and we have established a research program that is complex, comprehensive, multi-disciplinary, inter-disciplinary, and global. Further, this research investment is reaping even greater dividends, as AIDS-related research is also unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases. The legislative authorities of the OAR allow NIH to pursue a united research front against the global AIDS epidemic. NIH is enhancing collaboration, minimizing duplication, and ensuring that research dollars are invested in the highest priority areas of scientific opportunity that will

[17] HIV/AIDS Surveillance Report 2003, Vol. 15 (CDC, 2004).

allow NIH to meet its scientific goals. We are deeply grateful for the continued support the Administration and this Committee have provided to our efforts.

Senator SPECTER. Well, that is a good juncture to discuss that, Dr. Zerhouni. My colleagues look at the increases in the NIH budget and compare them with what is done generally or in other research lines, the National Academy of Sciences. NIH has gotten a much greater increase than anyone, and I think that's because this subcommittee has taken an interest in the subject and we have seen what you can do.

How can you quantify the good use of the money? Because many of my colleagues say, well, we don't know the details of NIH, but they've gotten too much money too fast to be efficient. Are you efficient?

Dr. ZERHOUNI. Well, this is——

Senator SPECTER. I know what the answer's going to be, but tell me why it's yes.

Dr. ZERHOUNI. I'm going to give you very simple numbers, sir. I believe in facts. Are we efficient? Do we have too much—have we received too many resources? $96 per American per year is what we invest in research and development and knowledge faced to a $5,500 per year spending in health care, rising at a much faster rate than inflation.

This ratio is really the key. We need to accelerate our knowledge so that we can change the paradigm of how we treat patients today. It would be more effective if we could develop methods of intervening years before the disease develops, rather than do what we do today, which is intervene after the disease has struck.

Senator SPECTER. Give me an illustration of that.

RESULTS FROM ACCELERATING OUR KNOWLEDGE

Dr. ZERHOUNI. A good illustration of that, I showed you the statistics on heart disease. You've seen how the mortality has dropped. That's because we've used as a preventive measure drugs that reduce high blood pressure and drugs that reduce cholesterol. Those two actions have led to a half of the reduction in mortality. That's a good example.

In stroke, we've reduced the mortality of stroke by 50 percent, just because we've used methods to reduce the impact of high blood pressure.

In cancer, screening for cancer, in colon cancers, is responsible for the majority of the reduction in mortality from colon cancer. So there are things we can do as we learn more about the genetics——

Senator SPECTER. Would you amplify your response on cancer?

Dr. ZERHOUNI. Well, in cancer you can see, for example, in breast cancer—I'll give you one example in breast cancer—with the use of tamoxifan and the use of new drugs, we've reduced the occurrence, the reoccurrence of breast cancer by 50 percent. We believe that in high risk populations, as we can identify them, and the National Cancer Institute is working on these factors, we'll be able to ultimately reduce the number of patients altogether who develop cancer. The same is true in colon cancer.

Senator SPECTER. How will you do that?

Dr. ZERHOUNI. Primarily by understanding——

Senator SPECTER. Why haven't you done it before now?

Dr. ZERHOUNI. I think we did not know the genetics of breast cancer or colon cancer until 10, 15 years ago. We started to know it, and our knowledge has accelerated over the past 5, 6 years with the completion of the human genome. We are continuing our efforts with the understanding of the genetic map and the continuing efforts and investments that NCI has put in understanding the genetics of cancer. That's the knowledge that allows us to do that.

Senator SPECTER. On this subject, we have with us today Dr. Andrew von Eschenbach, who's the director of the National Cancer Institute. Dr. von Eschenbach, would you step forward?

I might comment on the number of witnesses we had here because I had set at the outset that we have not followed the customary practice of having all of the directors where we couldn't possibly question more than 20 people who work in attendance. But Dr. Zerhouni and Dr. von Eschenbach are presidential appointees, and Dr. Zerhouni requested bringing Dr. Anthony Fauci and Dr. Allen Spiegel because of questions which might arise, and then we have added in, as I said earlier, Dr. James Battey because of the currency of an issue which has arisen on the application of the new ethics rules.

Dr. von Eschenbach.

Dr. VON ESCHENBACH. Yes, sir.

THE WAR ON CANCER

Senator SPECTER. You have the largest allocation in the National Institutes of Health, coming close to almost $5 billion. President Nixon declared war on cancer in 1970. Thirty-five years have passed and we've won some wars, but not that one. What will it take to win that war?

Dr. VON ESCHENBACH. Well, Mr. Chairman, first of all, the wisdom and the support that we have received at the National Cancer Institute from the Congress in providing the resources has led us to a point where in 1971 when we began this effort we did not understand cancer. We didn't understand that it was a spectrum of diseases, and we certainly didn't understand the basis of that disease. But today——

Senator SPECTER. A spectrum of diseases?

Dr. VON ESCHENBACH. Yes, sir.

Senator SPECTER. How many roughly?

Dr. VON ESCHENBACH. Well, there are certainly a large number of cancers, but what we're learning even today is that even when we think of one cancer like breast cancer or lymphoma, or even colon cancer, there are subsets of those cancers because of the fact that there are unique, different changes in the genes and the molecules that cause and drive that cancer——

LYMPHOMA

Senator SPECTER. How many subsets of lymphoma? I have a special interest.

Dr. VON ESCHENBACH. There are two major subsets of Hodgkin's and non-Hodgkin's lymphomas. But even within those groups, even as we speak, we are learning that there are subsets——

Senator SPECTER. Subsets within Hodgkin's lymphoma?

Dr. VON ESCHENBACH. Correct, sir, and especially in non-Hodgkin's lymphomas. For example——

Senator SPECTER. But how about subsets in Hodgkin's lymphoma? You'll pardon my special interest.

Dr. VON ESCHENBACH. Yes, sir. If you allow me, one of the ways that we're beginning to understand even what we think is a single disease of Hodgkin's lymphoma is to recognize that in different patients that lymphoma may have different molecules or proteins on the surface of the cell that cause it to behave differently and respond differently to different therapies or interventions.

For example, a recent drug that has been created is a drug that can attach itself to those proteins on the surface of the cell. One of those proteins is CD–20, an antibody. So if we can look at a Hodgkin's tumor and determine whether the antibody is present or not, we can then design and apply specific therapy for that specific patient.

RETURN ON INVESTMENT

To follow up on the question of the return on investment, this investment in cancer research that has led us to a point today where we're beginning to understand cancers at the molecular and genetic and cellular level is influencing our selection of therapy and moving us to personalized medicine and personalized oncology.

We're sparing patients unnecessary treatments that we can predict will not help them, while at the same time making certain we're giving patients the specific and exact therapy that we can predict and know at the molecular level will help them.

This drug I alluded to that's recently been released, Bexxar, combines the knowledge of that antibody, of CD–20, in a group of other lymphomas, non-Hodgkin's lymphomas, called follicular lymphoma. By identifying that antibody and coupling to it a radioactive material, we can target those lymphoma cells, and patients who were previously considered incurable now have a 75 percent complete response rate in elimination of their tumor.

Senator SPECTER. Before yielding to Senator Cochran, the distinguished chairman of the full committee I want to ask you one more question, Dr. Zerhouni, and you one more question, Dr. von Eschenbach. If we have a flat-level funding for NIH this year, how many grants will you have to reduce because of inflationary factors and other factors, contrasted with what you could do if we were able to get the extra $1.5 billion which is in the budget resolution?

SUCCESS RATES

Dr. ZERHOUNI. The total number of grants will decrease by about 400 total. As I said, we were going to make a special effort to increase the number of grants for new investigators or what we call competing investigators so that——

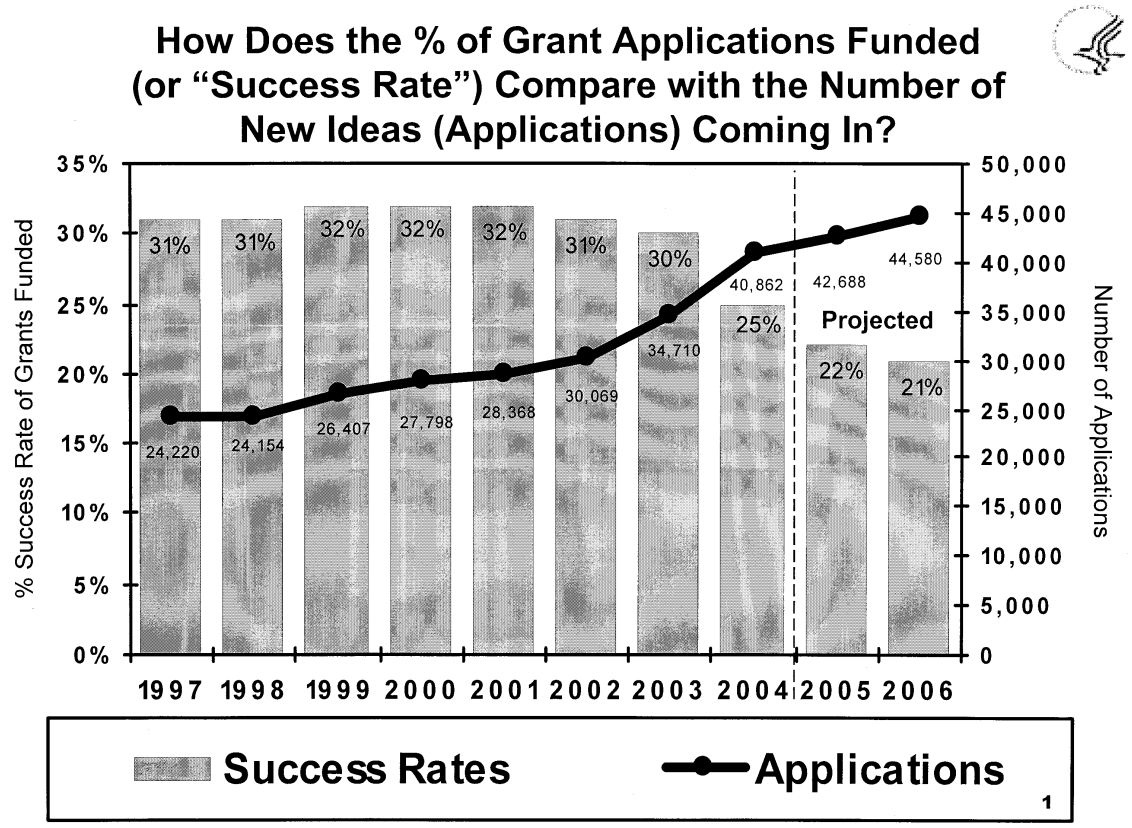
Senator SPECTER. With the extra $1.5 billion, then what?

Dr. ZERHOUNI. We could reestablish—you know, one of the things you said that is very important that we hear a lot is NIH has too much money, it cannot spend any more money. The best statistics I can give you is we are getting more and more ideas we cannot fund, and our success rate is actually dropping. I'll show you some statistics here that you can see, and we were at about 32 percent

a few years back to 30 percent to 25, 22, and eventually we will reach 21 percent in 2006. With——

Senator SPECTER. Of grants on applications, percentage that you grant?

[The information follows:]


How Does the % of Grant Applications Funded (or "Success Rate") Compare with the Number of New Ideas (Applications) Coming In?
% Success Rate of Grants Funded
Number of Applications
35%
30%
25%
20%
15%
10%
5%
0%
50,000
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
31%
31%
32%
32%
32%
31%
30%
25%
22%
21%
24,220
24,154
26,407
27,798
28,368
30,069
34,710
40,862
42,688
44,580
Projected
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006
Success Rates
Applications
1

Dr. ZERHOUNI. By those number of scientists we can fund when they apply, one in five, or a little bit above that. So clearly anything we could do to reestablish the ability of fulfill and satisfy the scientific demand would be helpful. However, we recognize as you did the very, very difficult fiscal times we're in.

FUNDING THE WAR ON CANCER

Senator SPECTER. Dr. von Eschenbach.

Dr. VON ESCHENBACH. Yes, sir.

Senator SPECTER. With sufficient funding, can we win the war on cancer in the reasonably near future?

Dr. VON ESCHENBACH. Senator, we have made a commitment at the National Cancer Institute to eliminate the suffering and death that results from cancer, to eliminate the outcome of cancer, and to bring that about as early as 2015 in this Nation. We have made that commitment because we believe that this investment that has been made in cancer research has led us to a point today where we can build on our understanding of cancer and use that knowledge to develop new and more effective interventions that can in fact achieve the goal——

Senator SPECTER. Do you have sufficient funding to reach that goal by 2015?

Dr. VON ESCHENBACH. The funding that we have we are applying as effectively and as efficiently as possible to achieve that trajectory. Obviously, with increase resources we have increasing opportunities to even further accelerate that pace of progress.

Senator SPECTER. If your funding were increased, could you reduce that date to 2010?

Dr. VON ESCHENBACH. We certainly could accelerate the pace of progress, and how quickly and how soon we could bring that about, I could not absolutely predict.

Senator SPECTER. I would like you to give that some thought and provide the subcommittee with a projection as to what kind of funding you would require to reduce the figure to 2010. A lot of people are going to have a lot of suffering in those other 5 years.

Dr. VON ESCHENBACH. Yes, sir.

Senator SPECTER. Really in the 5 years from now until 2010.

[The information follows:]

NATIONAL CANCER INSTITUTE

What would it take to accelerate the achievement of the NCI's 2015 goal to eliminate suffering and death due to cancer from 2015 to 2010?

You have requested information on the amount of money necessary for the National Cancer Institute (NCI) to achieve its 2015 goal by 2010. It should be noted, though, that these funding estimates for additional resources were developed without taking into consideration overall fiscal constraints and other competing priorities of NIH, HHS, or the rest of the Federal government over this five-year time period. The current annual NCI budget is nearly $5 billion, and the resources discussed below would be in addition to this base.

NCI has established an ambitious goal of eliminating the suffering and death due to cancer by 2015 by sustaining and integrating progress in the discovery, development, and delivery of more effective interventions based on molecular mechanisms of cancer. We estimate that expenditure of an additional $4.2 billion above the NCI base of nearly $5 billion over the next five years could accelerate progress. While the elimination of suffering and death due to cancer may not be fully achievable by 2010, there would be significant progress toward narrowing the gap between 2015 and 2010.

This $4.2 billion estimate reflects an additional up front allocation of $2.5 billion to be expended over five years for a National Advanced Technology Initiative for cancer (NATIc) to accelerate the emerging disciplines of molecular oncology, nanotechnology, and bioinformatics for use in creating a pipeline of new personalized cancer diagnostics and therapeutics. This would also reflect an annual increase of $171 million over current base NCI levels for five years to deploy a modern integrated cancer clinical trials infrastructure and an annual increase of $164 million for five years to expand and integrate the NCI-designated Cancer Centers program from 60 existing centers to 75. In addition to resources, additional legislative authorities related to exemptions from specific parts of current procurement, grant review and processing, and licensing and patenting rules would also help speed progress toward an accelerated cancer goal.

Three decades ago there were 3 million U.S. cancer survivors; today that number has increased to over 10 million. Today, each minute of every hour of every day, one American dies from cancer: 570,280 lives will be lost this year due to this disease. Despite this fact, there has been remarkable progress in understanding the cancer process and applying that knowledge. Today, 65 percent of patients diagnosed with cancer can expect to survive. If we had the ability to apply what we know today to every cancer patient, we could have an immediate impact on survival, largely through the NCI Cancer Centers. Incremental improvements in survival will continue toward our 2015 goal, but we can accelerate these gains. Even improving the overall survival rate to 90 percent by 2010 could mean an additional 850,000 lives saved. The impact of this strategy could produce annual changes in the first two years of around 2–3 percent, with larger increases occurring in 2008–10.

For most cancer patients, survival is greatly influenced by early detection. The rapid deployment of advanced imaging, nanotechnology supported early detection platforms and targeted therapies will change the face of diseases such as ovarian cancer, lung, colon and breast cancers; where survival is low because we can not currently detect them before they spread. Ovarian cancer, which is very difficult to detect and diagnose in its early stages, has over 25,000 new cases diagnosed annually and over 14,000 deaths; the mortality rate is nearly 85 percent. Imaging and detection techniques presently under development and broadly applied could reverse that mortality rate to be an 85 percent survival rate. Lung cancer, with approximately 170,000 expected deaths this year, would see a significant reduction in the number of deaths if the application of new technologies combined with other interventions could be universally applied in an accelerated manner.

The challenge to achieving the goal of eliminating the suffering and death due to cancer by 2010 is daunting, but with the authorities and appropriations commensurate with the task, the pace of progress could be accelerated, and the gap between 2015 and 2010 narrowed. The following reflects a brief overview of how such funds, if available, could be applied.

—Rapid Deployment of a National Advanced Technology Initiative for cancer—$2.5 billion one time appropriation with commensurate authorities.
—Deployment of a Modern Integrated Clinical Trials Infrastructure—$171 million addition to the NCI base budget.
—Expansion and Integration of the Cancer Centers Program—$164 million addition to the NCI base budget.
—Mechanisms and Flexibilities—streamlined procurement and review processes to acquire materials and services; coordination of licensing and patenting activities.

A National Advanced Technology Initiative for cancer (NATIc) could provide a linkage between the National Cancer Program and R&D initiatives being developed in selected National Laboratories and advanced technology facilities located in more than 40 states and regions. Connected in real time through a common bioinformatics grid, NATIc as a "network of networks" of science, technology, and treatment, could serve to accelerate the emerging discipline of molecular oncology to create a pipeline of new personalized cancer diagnostics and therapeutics from bench concept to bedside and community delivery. In the next few years, such an initiative could:

—Accelerate the implementation of a nationwide high-end information technology grid for bioinformatics that could be uniquely adapted for real time data sharing. NCI's pilot version, called caBIG, is currently being implemented among 50 cancer centers, the Food and Drug Administration (FDA), and other organizations.
—Develop a comprehensive biomarker discovery and validation program.
—Foster the application of emerging technologies, such as nanotechnology, and integrate molecular agents with advanced imaging devices.

—Accelerate a nationwide "real time" medical information electronic system for research and medical data sharing using technologies and devices currently employed by the banking industry and large-scale commercial enterprises.
—Enhance the discovery and validation of new targets of genes and proteins critical to cancer development.

NCI could deploy a more modem and integrated infrastructure for cancer clinical trials. This clinical research infrastructure could:

—Strengthen collaborations with industry, FDA, Centers for Medicare and Medicaid Services, and other public, private, academic, and patient advocacy organizations to oversee the conduct of cancer clinical trials.
—Develop new infrastructure and procedures to standardize, coordinate, and track clinical trials development and accrual across all NCI-supported clinical trials.
—Increase utilization of imaging tools in screening and therapy trials, evaluate new imaging probes and methodologies, enable access to the imaging data from trials in an electronic format, and facilitate evaluation of image-guided interventions.
—Expand access and improve the timeliness for completion of the highest priority clinical studies.
—Foster the development of a cadre of established clinical investigators who could work between bench and bedside.
—Pilot new approaches and develop prototypes for clinical trials networks that could improve the efficiency, coordination, and integration of our national efforts.
—Develop a common clinical trials informatics platform that could be made available to the full range of investigators working within the cancer clinical trials system.

NCI could accelerate the expansion and integration of the NCI designated Cancer Centers program, including the addition of 15 new cancer centers, increasing the number of centers from the current 60 to 75. The Cancer Centers program could:

—Implement progressive bioinformatics and communication systems to achieve horizontal integration.
—Fund additive programs in collaborative, multidisciplinary research, and require integration and sharing of results.
—Broaden the geographic impact of the centers, networks, and consortia and vertically integrate them with community and regional health care delivery systems.
—Improve the access of minority and underserved populations to state-of-the-art research and resources.
—Create and strengthen partnerships with government agencies and community organizations.
—Broadly provide expertise, and other resources to caregivers, patients and families, and appropriate health agencies.

In addition to appropriations, flexible legislative authorities related to exemptions from specific parts of current procurement, grant review and processing, and licensing and patenting rules could also help accelerate progress. A streamlined procurement process could facilitate the acquisition of materials and services to support the R&D activities. Technology development could also be enhanced by sufficient flexibility and integration to enable interactions among a wide array of laboratories and other entities. Expedited review procedures and workflow processing could help to award funds in sequence as needed. This might include direct solicitation from known laboratories or other sources of technology, and capability to terminate funding instruments at the convenience of the government with limited appeal processes so that funds could be redirected from low performing consortia to the more productive venues.

Coordination of the licensing and patenting activities among grantees, contractors and the intramural program could also be useful for many of the multi-component technology platforms that could be created through this effort. An accelerated process for Determination of Exceptional Circumstances (DEC) and deviations from appropriate Federal Acquisition Regulation (FAR) clauses, when deemed valuable to the broad research enterprise, could be utilized.

Senator SPECTER. Senator Cochran, thank you for joining the subcommittee.

STATEMENT OF SENATOR THAD COCHRAN

Senator COCHRAN. Mr. Chairman, thank you very much. We appreciate you chairing this hearing and also inviting Dr. Zerhouni and selected members of the National Institutes of Health staff who can help us understand the budget request and do our best to identify the areas that need emphasis in this budget. We appreciate your leadership on this subcommittee and on the full committee as well.

I notice that the budget request is $144.5 million over last year's appropriate level for the National Institutes of Health. I'm hopeful that that will permit the NIH to continue its research into health disparities, examining why a disproportionate number of African-Americans, for example, suffer from heart disease than the rest of the population. I think taking the research to the underserved areas of our country is beneficial. I hope you can let us know what your reaction to that initiative is at this point and what you foresee in terms of the needs for funding will be.

I think I'll stop at that point and let you respond, and I then have a couple of other questions.

STRATEGIC GOALS AND OBJECTIVES

Dr. ZERHOUNI. Those points are absolutely on target, Senator. As you know, we have five major goals that we have outlined in our strategic plans. One is aging of the population, the change from acute to chronic diseases. The third one is health disparity, not in any particular order. Those are amongst the five. And then we have biodefense and emerging and re-emerging diseases, including, for example, obesity.

We're acutely aware of the disparate impact of these conditions on the American population. As you know, we have the vanguard study in the Jackson heart study that in fact studies how to do this better. As part of the Roadmap for Medical Research, we are also developing the idea of a community-based corps of clinical researchers that will be included within the underserved areas of the country and connected through a better information system, so that more patients in those communities can participate.

A good example of that, Senator, was the ALLHAT study, which was the study of hypertension conducted in over 600 practices. A great majority of the practices were in African-American communities and showing which drugs were the most effective in those populations.

So we will continue that. I think the investment needs to be continued, Senator. This is not an easy problem to tackle, but we need to look forward to more activities that will integrate the main research that we do with the research that needs to be done in those communities.

COMPLEMENTARY AND ALTERNATIVE MEDICINES

Senator COCHRAN. One other interesting new area of inquiry for the National Institutes of Health is in the area of dietary supplements and herbal products. There is a growing number of Americans using these supplements and products. The National Center for Complementary and Alternative Medicines is playing a role in

helping us understand the effects of that activity and the use of those products.

What are the current research needs or priorities in terms of this budget request that we need to consider when we are reviewing the request and deciding on the amounts to appropriate?

Dr. ZERHOUNI. First and foremost is your statement about the increasing use of dietary supplements across our population is real. Herbal products are becoming very popular. One of the things we need to do as scientists is to figure out whether or not these products are of equal effectiveness across their compositions. So we need to have more research done in exactly how to make these herbal products reliable and safe.

We are doing that at NCCAM. We verify the purity of these herbal products. We also have trials verifying their effectiveness. This year NCCAM and the Office of Dietary Supplements are going to fund five new botanical research centers across the country. There is a request for applications that has gone out. We've received the applications. So we'll have at least an infrastructure now of five centers that will look exactly at these issues of how do you really make sure that when you buy a particular product it's effective for what you think it is effective for.

Senator COCHRAN. My final question has to do with the role for new technologies in the detection and treatment of disease. For example, the National Institute for Biomedical Imaging and Bioengineering was created specifically to enhance research on these technologies across the NIH Institutes. What budget levels are needed for this work to be done and to improve the rate of discovery in biomedical research across the Institutes and increase the development of new tools for diagnosis and treatment in clinical practice?

NATIONAL INSTITUTE FOR BIOMEDICAL IMAGING AND BIOENGINEERING

Dr. ZERHOUNI. This is newest Institute, as you all know, that is essentially going through its strategic first steps. It is the only Institute that has for a mission the interaction of technologies, physical sciences, biological sciences, in the context of bioengineering or biomedical imaging. In that regard, it is very important to continue to invest, because as we see, you know, when we look at detection, for example, of new diseases, new technologies to do research, it's becoming very apparent that we need to make specific investments in those areas if we are going to make progress in both detection and therapy.

For example, nanotechnology is a good example whereby you can through nanotechnology techniques concentrate energy inside a tumor and treat a tumor in a way that you couldn't otherwise. NIBIB is key to that interface. It's taken a role, a lead role, in matching physical sciences and biological sciences at NIH, works with the National Institute of General Medical Sciences.

Obviously, the budgetary environment is such that they have to make very tough choices in terms of prioritization. But from my standpoint, Senator, emerging research technologies, I see that and we've identified in the Roadmap for Medical Research, as a major area of investment. In the past, biomedical researchers tended to

wait for technology to be developed and then used it off the shelf, whether it be computers or robotics or other technologies.

In the future, as we are going to areas of research that are only specific to medical research, no one in the free market is going to develop an off-the-shelf technology that will have just application to medicine. And therefore, NIBIB's strategic role has to increase over time, and all of NIH's investment in that area.

Senator COCHRAN. Thank you very much. I appreciate your leadership in these areas that I've touched on and generally at NIH. I think you're doing a great job and we appreciate your service.

Dr. ZERHOUNI. Thank you, Senator.

Senator SPECTER. Thank you very much, Senator Cochran. I'm now going to yield to the distinguished ranking member, Senator Harkin. I'm going to go vote and I will return promptly so we can maintain the continuity of the hearing.

Senator HARKIN [presiding]. Thank you very much, Dr. Zerhouni.

Dr. ZERHOUNI. Good morning.

Senator HARKIN. I apologize for being a little late for your presentation. Obviously we all have a lot of committees we have to go to. But I just wanted to make a brief opening statement and welcome you back and the others back.

As you know, Dr. Zerhouni, both Senator Specter and I have been very strong supporters of NIH and funding. We've partnered in doubling the funding for NIH over 5 years. We got that job done. It was one of my proudest moments as a Senator to actually get that accomplished.

Yet as I look at the President's budget for 2006, it's with a sense of disappointment. We didn't double the funding for NIH to then have the bones cut out of the funding. But that's what it seems is happening. This budget would provide the smallest percentage increase since 1970, .5 percent. The total number of grants would drop by 402. Most importantly, the success rate for new and competing grants would fall to 21 percent. I have the table here. I guess you put it up here. I missed it, but my staff told me you put it up here. Twenty-one percent, that's the lowest since 1970, and that's as far back as our records go, 21 percent. This is very disturbing.

Our scientists have just mapped the human genome. We should be entering a golden age of medical research. Scientists should be flocking to this field. It's the wrong time to hold this budget flat.

I'm also troubled by other developments. Top researchers are leaving NIH. Recruitment is suffering because of new conflict of interest regulations. While I strongly support restrictions on outside compensation, I am concerned that the new regulations go too far, Dr. Zerhouni, especially when it comes to requiring employees to divest stocks that they've had for many years.

I just, as an aside, ran into a woman yesterday, just yesterday afternoon. The AACI group had a reception yesterday and I was just talking to a woman. I mentioned this hearing and she mentioned how it was her sister, I believe, was a researcher at the National Institute of Environmental Health Sciences in North Carolina, had been there for a long time, is leaving because through the years she said the most income she and her husband ever had was $125,000 a year. Lately, because she's worked all these years, she

bought some stock early on, that's her retirement, that's for her kids going to college, and according to her—I don't know, I'm just telling you what she told me—she has zero input to any kind of drugs or drug companies or anything. Yet she's told she's got to divest that stock. You know what? She's leaving. That's wrong. That's wrong. We've got to change this, Dr. Zerhouni. We've got to change this.

I look forward to working with you and I'll have some more questions about that.

Jim Battey, who's leaving, has been a great researcher, great leader. I've worked with him on deafness and communication disorders. As I understand it—I don't mean to get into all this personal stuff—but I understand there's a family trust set up that he has to administer and stuff like that, and he has to leave because of this. This isn't right. We have to have a change and we have to have a change soon, immediately.

Now, let me just switch to something else, and that's the whole issue of stem cell research. The administration's outdated policy on stem cells is making NIH increasingly irrelevant in one of the most exciting areas of research today. We know about California putting in $300 million a year. NIH is spending less than one-tenth of that amount, NIH one-tenth the amount of one State. Inevitably, researchers are going to look to individual States for direction on stem cell research instead of the NIH.

What's happening to NIH? Is it just a shell of its former self? It's supposed to be the greatest biomedical research institution in the world. I'm beginning to wonder.

Our federally funded scientists are on the front lines in the war against cancer and heart disease, diabetes, on down the line. To me there is no higher priority in this appropriations bill than funding NIH at an adequate level.

So that's my opening statement and I just want to return to the conflict of interest rules. Now, you know I have the greatest personal admiration for you and friendship. I think you're doing a great job in leading the institution. But I must chastise you. These are too onerous. They've got to be redone, and they've got to be redone soon before you start losing more people out of there. I mean, you know, sometimes we tend to see a conflict of interest and we go overboard, and I think we've gone overboard here.

So I'm just asking, are you prepared to recommend to HHS that the Department issue new revised regulations that won't hurt NIH's ability to retain and attract top scientists?

PENDING CONFLICT OF INTEREST RULES

Dr. ZERHOUNI. Well, I'm glad you asked the question, because as you know, this has been a painful episode for NIH where we've looked at several hundred issues that came up through the activities of scientists for private pay with biotech and pharmaceutical companies, as you were concerned about. From my standpoint it was very important to take care of that issue, and we did.

We proposed the moratorium because I think there were two reasons there that prompted me to do that. One was the fact that there were activities there that truly did not advance research. They were more into the marketing and product endorsement ac-

tivities. I thought that we needed new guidelines. Second, I believed that our management system of ethics was not functional, and to establish a new one, to re-centralize it, takes a while.

Now, you should know that these rules and regulations are not under my direct authority.

Senator HARKIN. I understand.

Dr. ZERHOUNI. They are those of——

Senator HARKIN. I misspoke. It's HHS.

Dr. ZERHOUNI [continuing]. HHS and the Office of Government Ethics. We've consulted with them and indicated to them that some of the applications may need to be tested on the ground. That's why we insisted that these be called interim final regulations and they be subject to comments and evaluation and adjustments. I have to say that I'm as concerned as you are.

Remember that at this point the most impact I have seen, because the rules have not been implemented in terms of stock divestiture, is the impact on families and the impact on all of the employees that would be required to divest of stock. That part of the rule frankly is the one that I think we need to reevaluate very quickly, as you said. I have requested a delay in the application of this rule from Secretary Leavitt, who's been extremely responsive and extremely concerned about any impact.

In the preamble to the rule, as you may know, we have stated very clearly that the Department and NIH will carefully look at the impact on retention and recruitment and the impact on the activities of our scientists in terms of outside activities.

So we are totally prepared to look at that, I am totally prepared to look at that, and request from those who have the authority—the Office of Government Ethics and the Department—to consider changes. So far I would say that, number one, we've had a responsive interaction. Number one, we've had a 90-day delay, and no one has been asked to divest at this point.

But nonetheless, the uncertainty itself can be damaging to morale and damaging to recruitment and retention. You've mentioned the example of Dr. Battey, who's a very good colleague of mine, an outstanding scientist, and I understand very much his predicament and I've made that known to the Secretary and to the Department.

There's another case, as you know. I've taken a lot of time and effort in recruiting outstanding directors. When I became director there were six vacancies and two others. I was very proud of the fact that we've been able to recruit outstanding directors from outside of the NIH and inside of the NIH. The latest one was Dr. David Schwartz from Duke University, who last week sent me a letter saying that he was delaying his coming until this issue of stock divestiture is clarified.

So I feel the same way you do in the sense that the philosophy of the interim regulation as promulgated by those who promulgated that with our consultation is in my view one that would be more appropriate for a regulatory agency rather than a scientific agency, and does require in my view more selective approaches rather than these approaches.

I think the Department has been responsive. As you may know, the Department has excluded trainees from these rules. That's over 5,000 scientists who are not subject to these rules. However, we've

also encouraged our scientists at NIH to come forward. I've had multiple meetings with scientists who are very concerned about this, and gotten their comments, and based on those comments we'll adjust accordingly.

So I share your concern and I do believe that, as you will see, we will be adjusting accordingly to correct for that issue, which I think is the one that is at the core of the complaints that you've heard. But also I am concerned about any impediments that free academic exchange might incur because—with trade associations—because of this over-regulatory interpretation of what NIH does. I don't think NIH has the influence of a regulatory agency, and I think as we go through the evaluation comment period, you will see improvements in that, Senator.

Senator HARKIN. I appreciate that and I apologize for misstating. Sometimes I look out there I just see HHS, and I said—I meant not you but the whole Department——

Dr. ZERHOUNI. It's okay. I'm used to it.

Senator HARKIN. The whole Department for what they did. But we——

Dr. ZERHOUNI. I'll take responsibility for——

Senator HARKIN. We've got to settle this. I'm sorry. I've got to go vote, and I assume Senator Specter will be right back, and so the committee will stand in recess until the chair gets back.

Dr. ZERHOUNI. Thank you.

Senator SPECTER [presiding]. The hearing of the Appropriations Subcommittee on Labor, Health, Human Services, and Education will now proceed.

Dr. Zerhouni, at the outset I thanked you for the assistance which NIH has provided on an arrangement with the Institute of Medicine to fund an examination of certain areas of asbestos-related injuries. We are trying to put through an asbestos bill and there is a question as to whether there is a causal connection between asbestos and certain ailments, and the Institute of Medicine has agreed to expedite a study in the course of 1 year. I worked with Dr. Raynard Kington in your absence and we were able to work that out expeditiously, and I thank you for that.

Dr. Zerhouni, let's turn to the issue of the guidelines on ethics and the concerns which have been expressed by some. And I'm going to want to hear from—we're going to want to hear from Dr. James Battey in a few moments as to the range of the restrictions which have been imposed and the reaction and whether you think there might be some justification for a review of the standards and practices.

GUIDELINES ON ETHICS

Dr. ZERHOUNI. Senator, first and foremost, the rules as we have—as they have been promulgated by the Department of Health and Human Services and the Office of Government Ethics are interim final regulations. In that process we made it very clear that those rules will be subject to an impact analysis and a comment period, especially when it comes to recruitment and retention areas and the maintaining of the excellence of the science at NIH.

Now, as you know, when we developed the rules there was a component of the rules that was related to consulting with indus-

try. I believe that the rules that we have put in place do establish and re-establish public trust and maintain public trust in that we will ban those until we are completely certain that we have an oversight system that is more functional than the one we had before.

Senator SPECTER. Do they go too far?

Dr. ZERHOUNI. In that context—in the consulting area, I think this is something that we need to do because we do not have, I believe, at this point an ethics oversight management system that can assure you and assure myself that those interactions are——

Senator SPECTER. How about in areas other than consulting?

Dr. ZERHOUNI. In areas such as stock divestiture, as you know, the rules require that all employees and their spouses divest of stock in either directly or indirectly related industries of NIH. As I looked at that rule over the past 2 months, I've had extensive consultation with our scientists, with outside entities, directors of the Institutes, and it is clear to me that in the short 2 months, where these rules have not been implemented by the way, no one has been asked to divest, that this would have a deleterious impact. Best example, as you mentioned, is Dr. Battey, who really cannot disentangle himself from his family obligations; Dr. Schwartz, who's the new director that I just appointed and recruited from Duke University, who was to take his job on April 11, who has delayed his coming until we can understand these rules a little bit better.

Senator SPECTER. How about the issue raised that someone couldn't accept train fare to travel to a distant city to give a lecture?

Dr. ZERHOUNI. That is not correct. I've heard that. That, Senator, that is not correct. People can accept train fares, hotel reimbursement when they go to do an academic lecture at some other points.

Senator SPECTER. Is there any other area besides consulting and divestment on a broad category?

Dr. ZERHOUNI. I think the interaction between our scientists and trade associations, scientific associations, should not be hampered to the extent that we have seen them being hampered over the past two months. We need to work on that.

I have to tell you, Senator, that Secretary Leavitt has been very responsive and receptive. We've requested a delay in the implementation of the stock divestiture rule of 90 days so we can understand it better. We have also asked that all of our scientist trainees, 5,000 of them, be exempted from these rules.

So, again, I think we do believe that through this process of comments and evaluation that we have put in place in the interim final regulations, that we will be able to adjust accordingly.

Senator SPECTER. How about on the trade association issue?

Dr. ZERHOUNI. Right.

Senator SPECTER. How about on the trade association issue?

Dr. ZERHOUNI. Again, I think, Senator, from my standpoint, if you look at the framing of these interim final regulations, they make an assumption that NIH has the same influence as a regulatory agency. In that context obviously these interactions have to be scrutinized, but I don't at this point have a final opinion, but

it seems to me that they may restrict areas of academic interchange——

Senator SPECTER. So you do not have a final opinion, so you're still looking at that?

Dr. ZERHOUNI. We're still looking at that, but I do believe that we should not as a policy goal restrict interactions that are purely scientific or academic in any way, shape or form.

STOCK DIVESTITURE

Senator SPECTER. Let us hear from Dr. James Battey, if we may. Dr. Battey, thank you for joining us. We know that there has been an issue as to divestment which has been problemsome for you with retention at NIH. Would you tell the subcommittee your situation?

Dr. BATTEY. Absolutely. But let me preface my remarks by wishing you Godspeed in recovering from your illness, Senator Specter.

Senator SPECTER. Well, thank you. Thank you.

Dr. BATTEY. I have the greatest job in the world as far as I'm concerned right now. I've been the Director of the National Institute on Deafness and Other Communication Disorders for 8 years, and I have enjoyed every single minute of it for 8 years. But I manage a family trust on behalf of my mother and father, it's their sole source of income, as well as my two sisters, as well as educating my father's seven grandchildren. That is a responsibility that I must put before even the greatest job in the world. I cannot divest the stocks in that trust. The cost to my family would be very, very substantial, and that is not something that I am willing to entertain on behalf of my sisters, my father's seven grandchildren, and my mother and my father.

Dr. ZERHOUNI. I should point out, Senator, that Dr. Battey at no time had any consulting activity with industry during his entire career. He's been one of the outstanding citizens of NIH.

Senator SPECTER. Well, Dr. Zerhouni, did Dr. Battey's situation run afoul of the ethical guidelines which have recently been established?

Dr. ZERHOUNI. Not all of them obviously. It really relates specifically to the obligation to divest, forced divestiture of all holdings related to the industries that relate to NIH.

Senator SPECTER. Well, is that rule——

Dr. ZERHOUNI. That's really what the issue is.

Senator SPECTER [continuing]. In effect at NIH?

Dr. ZERHOUNI. This rule is not in effect. It is proposed to be implemented by July 3. We have asked the Secretary and received a delay of 90 days. It was supposed to be activated 2 months after the beginning of the rule on February 3. It was clearly obvious to us at NIH that this would have a deleterious impact. We've been requesting and informing the Department, I believe that the Secretary by delaying the implementation of this part of the rule, the forced divestiture, by 90 days, is giving us the opportunity to adjust accordingly.

Senator SPECTER. If, Dr. Battey, if this rule is not promulgated and become final, can we save you from California?

Dr. BATTEY. There are a set of circumstances under which I would entertain remaining with the National Institutes of Health.

As I said before, I love this job, I think it's the greatest job in the world.

Senator SPECTER. Well, we will leave to Dr. Zerhouni the exploration of those set of circumstances. But my telephone number is in the book.

Dr. BATTEY. Senator, I very much appreciate your support.

Senator SPECTER. Because as I had said earlier, very much concerned about the impact and I'm not faulting anyone. This is a tough area to move in, and there are bound to be unintended consequences. But with your record and your reputation, it would be very unwise, not helpful, to have the NIH lose you on this issue. I'm glad to see that Dr. Zerhouni and the others who are promulgating the rules are having a delay and will take these issues into account.

Dr. BATTEY. Thank you. Let me just add that I agree 100 percent with Dr. Zerhouni that it is absolutely essential that the Agency maintain the public trust and be a neutral broker in the eyes of all those who consult with us and ask us to give opinions in the area of biomedical research.

Senator SPECTER. Well, I'm pleased to hear you say that, and let's see if we can't get it to work out to retain Dr. Battey and move ahead with the ethical guidelines in ways which are really meaningful and necessary.

STEM CELL RESEARCH

Before Senator Harkin returns, Dr. Zerhouni, just a question or two about stem cells. Where are we heading? Are we going to be losing all of our stem cell geniuses to Europe, to California, to Massachusetts?

Dr. ZERHOUNI. California right now is probably the State that has the most wide-ranging policy allowing research in the field of regenerative medicine. Clearly, when you look at the scientific evolution of this field, and as I've said before, from the purely scientific standpoint, there's no doubt that access to more cells is seen by scientists as very important to their progress.

Much can be done with the cells available through NIH and they're federally funded through the current policy. However, it is clear that when you look forward, NIH is funding about $30 million worth of human embryonic stem cells and over $390 million total in regenerative medicine. The California investment is about $300 million total, not just in embryonic stem cells. So it's not fair to say that the Federal investment is one-tenth of the California investment. That relates to the human embryonic stem cells. The California investment is not specific to just human embryonic stem cells.

Senator SPECTER. Dr. Zerhouni, why shouldn't we utilize the stem cells which are frozen, several hundred thousand created for in vitro fertilization? They have the potential to save lives. Why shouldn't we use them for scientific research?

Dr. ZERHOUNI. From the purely scientific standpoint, scientists will tell you, I will tell you that there are areas of research that could be advanced, especially when you look at the 22 cell lines that we have. There is mounting evidence that we have contamina-

tion issues that may prevent their use for clinical applications, other issues of genetic stability are also emerging.

Clearly from the purely scientific standpoint, more cell lines may well be very helpful. The issue is not a scientific issue, as you well know. The issue is the policy is predicated on a moral and ethical line that says that we could not use Federal funds to remove the potential for life of these embryos.

Senator SPECTER. Well, what is the moral and ethical line if they're going to be destroyed? If they could create life—Senator Harkin and I took the lead in appropriating funds for embryo adoption. People would take the embryos and utilize them to produce children, people. But if they're going to be destroyed, where is the moral issue?

Dr. ZERHOUNI. I think you'll have to ask that from those who hold that view. I mean, obviously there are—there is a polarization of views on this issue. Some believe very strongly that an embryo is the beginning of life, and therefore, any use of that is inappropriate. Others obviously see the good on the other side. Every ethical issue is a balance between a social good and something that is seen by some as destructive.

I think that debate needs to go on, needs to occur. It is occurring, I think, amongst yourselves as legislators. From a purely scientific standpoint we believe, and we've said so, that more lines may well be helpful to this research.

Senator SPECTER. The legislation which Senator Harkin and Senator Feinstein, Senator Hatch, Senator Kennedy, and I have introduced bans cloning. We have the issue of nuclear transplantation, which does not come near the question of cloning. There are reportedly remarkable opportunities on nuclear transplantation to provide cures for the individual himself, herself, whose bodily substance is satisfied. Why not, Dr. Zerhouni?

Dr. ZERHOUNI. Well, again, the issue here is Federal funding being used on the one hand to use discarded embryos, as you mentioned. Then the other is somatic cell nuclear transfer where you create an embryo. The issue here is fundamentally the use of Federal funds for this kind of research. It's not a scientific issue.

Senator SPECTER. Well, I know the issue. The President's policy permits the use of some lines developed up to August 9, 2001. But there is growing evidence that the stem cell lines available on the NIH registry are showing epigenetic and genetic changes in small regions of the chromosomes. This is a prepared statement, Dr. Zerhouni, so I'm reading. Deputy Senator Taylor just made this available to me and I want to ask you the question.

I've been instructed to ask you this, Dr. Battey. When I get an instruction from Bettilou Taylor, I take it.

Dr. BATTEY. I think that's very well-advised, Senator.

FEDERAL FUNDING FOR STEM CELL RESEARCH

Senator SPECTER. Well, this is a joint question from Ellen and Bettilou and Tom and Arlen. All of those lines are being used to study basic biology of stem cells. Their use in clinical applications is questionable. There is confusion among scientists and administrators at universities where scientists have both Federal and nonfederal funding for stem cell research about exactly what research

infrastructure or core facilities developed with NIH funds in the past can be used in studies involving stem cells not eligible for Federal funding.

Dr. Battey, in addition to the position which you identified, and until last week you were chair of the NIH Stem Cell Task Force, what is your view of the current limitations of Federal funding?

Dr. BATTEY. Senator, the state of the science is moving very, very rapidly here, and we have learned many things since the last time I had an opportunity to testify before this subcommittee. For example, scientists at the University—or in the city of Chicago have now made stem cell lines from embryos that were identified in pre-implantation genetic diagnosis to harbor mutations that cause disease.

These stem cell lines could potentially be used to create cellular model systems that would allow the development of drugs to treat these diseases. I'm talking about diseases like muscular dystrophy and Huntington's disease. These cell lines, however, were all created after August 9, 2001, and are therefore ineligible for Federal funding.

The issue you mentioned about funding streams, it's a real issue. Let me give you an example. Imagine for the sake of argument an investigator who has a cell line he got from Doug Melton, it's not eligible for funding, and a cell line from Wisconsin that is. That investigator extracts messenger RNA from those two cells and then wants to go to his core facility for doing a study of what's been expressed in terms of gene expression that was funded initially by support from the National Institutes of Health. Can that investigator analyze that sample in that facility?

These are the sorts of complex issues that are now arising on a daily basis in places where there are substantial amounts of funding for stem cell research that is outside the confines of that which can be funded using Federal dollars.

Senator SPECTER. Well, thank you very much, Dr. Battey. Senator Harkin has this on his agenda, and I'm going to excuse myself at this point and turn the hearing over to my distinguished colleague, Senator Harkin. We often say that when the gavel changes hands, it's seamless. Show them, Tom. We have had a unique partnership in this contentious Senate and Congress to put aside party differences in the interests of moving ahead on a factual basis. I think the American people are really sick and tired of the bickering, and Senator Harkin and I have, I think, established the kind of a relationship which is in the public interest. It's all yours, Tom.

Senator HARKIN [presiding]. The only follow-up I had with Senator Specter's question for you, Dr. Battey, was on the scientific basis of this. Now, I don't know what all these words mean, but your statement says: "there's growing evidence that the HESC lines available on the NIH human embryonic stem cell registry are showing epigenetic and genetic changes in small regions of the chromosomes." Please explain what that means.

EXPLANATION OF EPIGENETIC AND GENETIC CHANGES

Dr. BATTEY. I'll try to explain as best as I can. A genetic change, Senator, is an actual change in the order of bases in the DNA sequence itself. An epigenetic change is a change that involves mark-

ing on those DNA bases that have implications for which genes get expressed and under what circumstances. What is becoming increasingly apparent is that as the cells are cultured for prolonged periods of time, we are observing both small genetic changes as well as epigenetic changes. This does not come as any great surprise to a cell biologist, and in fact is observed almost any time you culture cells for prolonged periods of time.

The reason for that is, although all the words are complicated, the reason is very simple and easy to grasp, and that's that when you grow cells in culture, you are continually selecting for a more rapidly growing cell. That is intrinsic to the process of passaging and growing cells.

So it is inconceivable to me that you would not evolve changes that would confer a growth advantage as you culture cells over prolonged periods of time. In fact, what is remarkable is how stable these embryonic stem cell lines are over time. The fact—but nevertheless, these changes will evolve if you culture the cells for maybe 50, 75, or 100 passages.

Senator HARKIN. To my layman's mind, it seems what you're saying is that somehow this would affect their use in any kind of further down-the-road treatment in humans?

Dr. BATTEY. That we don't know. That is not clear yet. If the changes, however, move the cell towards a more rapidly growing state, it is possible that you would have a cell that would evolve a genetic change that would take it one step closer to becoming a tumor of the stem cells, which is a teratoma. I think that's the major concern.

Dr. ZERHOUNI. Senator, the best analogy—sorry.

Senator HARKIN. No, go ahead. Yes, please.

Dr. ZERHOUNI. The best analogy to this is the one I had to come up with to explain this in layman's terms. That is that if, suppose you have an original document and you want to make Xerox copies of that document, and you make billions of copies each generation from the previous document. What may happen is that after the 150th generation, after making billions of copies of the DNA, you'll have errors, and you'll have a poorer copy and a poorer copy and a poorer copy as you go forward.

At the onset of this field, 5 or 6 years ago, everyone thought that stem cells were renewable in a perfect state, as if you had a perfect copy each time. Well, as the science has advanced and our methods of measurements have become more accurate, we are finding that in fact there are errors that occur over the transmission of information through that copying process. That may, in fact, have profound implications as to the viability of an experiment and the viability of the use of these over a long period of time.

Senator HARKIN. Again, in my layman's mind, it sounds like that argues for getting as many stem cell lines as possible.

Dr. ZERHOUNI. From a scientific standpoint, I think there are lots to be learned. In addition to the new science that has occurred recently, in terms of disease-specific cell lines that could be used such as the lines that Dr. Battey mentioned that have specific diseases in them, so that you could use that to study that disease process in a laboratory. From the scientific standpoint, this might be helpful.

Senator HARKIN. I just had a couple of other questions that I really wanted to go over here. Dr. Zerhouni, one of them had to do with, again, the success rate down to 21 percent overall. I noticed that at NCI, National Cancer Institute, it's 19 percent. At NCCAM it's 8 percent. I'm concerned about, again, what message this sends to young investigators who have a particularly hard time winning grants when money gets tight.

If a young med school student with huge loans to pay knows he faces only a 1-in-5 or a 1-in-10 chance of getting a grant, he or she may want to think twice about whether they want to enter this career. Would you just speak if you can for a little bit on the impact that you might see that a 21 percent success rate would have on your ability to attract young scientists to medical research?

NATURE OF SUCCESS RATES

Dr. ZERHOUNI. Again, the 21 percent success rate reflects two facts. One is the doubling has been very successful in attracting a larger number of excellent scientists to NIH. So the number of applications has in fact increased over time. I wanted to show you again the graphic there. The black line shows the number of applications rising all the way to 44,000. So we have more—go ahead.

Senator HARKIN. Now, are those applications or are those peer-reviewed applications that are——

Dr. ZERHOUNI. Peer-reviewed applications.

Senator HARKIN. Peer-reviewed.

Dr. ZERHOUNI. Right. The applications——

Senator HARKIN. Not the total. These are just the——

Dr. ZERHOUNI. These are the ones that are peer-reviewed by NIH that are——

Senator HARKIN. Made it through.

Dr. ZERHOUNI. Made it to review. Of those, we funded 32 percent in 2001, 25 percent in 2004, and 22 and 21. Obviously if the number of applications had stayed level, our success rate would have been higher. But the fact is we have more areas of research that we are into today than we were 5 or 10 years ago.

Now, your concern about young scientists is my concern as well. As you may know, I have requested a study from the Institute of Medicine. Two years ago we engaged our advisory councils about the issue of the lengthening of the time it takes for a young scientist today to be independent and to have their own research ideas worked on. Thirty years ago, 27 percent of our NIH grantees were 35 years or younger. Today, less than 4 percent of our NIH grantees are 35 years or younger.

That reflects two things—I'm sorry.

Senator HARKIN. What was that year cut-off?

Dr. ZERHOUNI. 30 years ago.

Senator HARKIN. 30.

Dr. ZERHOUNI. 27 percent of our scientists 30 years ago were younger than 35 years of age. Today it's 4 percent. On average when you look at the first grant, median is about 39, 40 years of age. This to me is a little too long. I really believe that there is a lot of creativity that occurs early in a scientific career.

The effect is twofold. One is the lengthening of the training period, but also the competitiveness of our grant process. That's why

a 21 percent success rate, if not balanced by new grants, as I've done, and if not carefully managed, can lead to a loss of talent.

Think about it this way, Senator. If you're a 25-year-old scientist and you look at your career and you have to wait until age 39 to have a chance to get a grant from NIH, you might consider other career tracks. That to me is the one thing that I worry the most about. We're going to consider very carefully the IOM recommendations and try to do the best we can within the fiscal constraints that we have.

But I think it is a trend, Senator, that all of us have to be aware of, and that is the plight of the young scientist, not just in biomedical sciences, by the way, Senator. It affects science and technology in general.

Senator HARKIN. It seems to me in my memory bank someplace, that this has been a discussion point in the past. Do you have a fund in the Director's office or something like that where—who was it termed it the "ah-ha" fund? Some young scientist says ah-ha, I got this idea, and you can kind of pick some of these young people and say, oh, they're on to something maybe, maybe, we don't know. But don't you have some fund like that? Is there something at NIH that allows that to happen under your direction?

VARIOUS SOURCES OF FUNDING

Dr. ZERHOUNI. I do not have a fund for that. But through the Roadmap, we've established a Pioneer Award to try to in fact encourage that, to try to find out if there are scientists out there that we're not funding through the process.

Institutes themselves, by the way, through loan repayment programs, career award developments, K–22 awards, all kinds of mechanisms are responsive to a different degree to this issue of the young scientists. We have Shannon awards, which provide a young scientist with transitional dollars.

I think, as the IOM recommends, it's time for us to look at all of our policies across NIH and find out, especially in tougher times, what we need to do proactively to in my view protect the pipeline of talent that 20 years from now will be the discoverers of the new cures and new treatments and new knowledge that we need.

We have a retreat with the NIH directors planned later this year to talk just about this as well. We have discussed this issue amongst ourselves quite a bit, as we are concerned about it.

AVIAN INFLUENZA

Senator HARKIN. I'll look at that some more myself, see if there's some way we can set something up like that. There were a couple of other areas I wanted to cover, one for Dr. Fauci and one for Dr. von Eschenbach. I'll start with Tony.

A lot of stuff being written about avian flu. Why is the spread of this avian influenza so alarming? What steps is the Institute taking to address this issue?

Dr. FAUCI. Well, thank you for that question, Senator Harkin. It's a very important public health issue. The concern surrounding the avian flu threat that we are currently undergoing now relates to the fact that the situation in countries in Southeast Asia, particularly Thailand, Vietnam, and to a lesser degree Cambodia, is

that there a virus called H5N1 circulating among chicken flocks. That is the way we designate influenzas by an H and an N, which are two of the proteins that are the important identification markers.

The regular flu that's circulating around this winter was an H3N2, a totally human influenza virus. The H5N1 is a bird flu. It has been infecting and killing large numbers of chickens in Asia. But what has happened over a period starting from the first identification in 1997 in Hong Kong of H5N1, which infected 18 people by jumping from the chicken to the human, and killing six of those, over the past year-and-a-half, in 2003 and now in a very accelerated way in 2004 and 2005, we've now had larger numbers of chickens infected and larger numbers of people. As of last night's count, there were 79 official cases confirmed and 49 official deaths confirmed.

Now, that may seem like a small number, but first of all, the mortality is very high, and second, there's a transition of the viruses getting a greater efficiency of spreading from the chicken to the human. Then what we're very concerned about is human-to-human spread. That has not occurred efficiently up to this point. There is at least one documented case in Thailand of a mother who got it from her 11-year-old child who, the child got it from the chicken, but the mother actually got it from the child.

If there is increased efficiency of spread from person to person, we have the possibility of what we call a pandemic. Now, that means that the society in general, our civilization, doesn't have any baseline immunity to H5N1, because unlike H3N2, where each year we get exposed to one variety or another of that strain, we get vaccinated or we get infected, so that our society has some degree of background immunity to an H3N2. We have zero background immunity to H5N1.

So the possibility of there being rampant spread, particularly with the high mortality that we're seeing right now, is a very sobering prospect that we're looking at. What are we doing about it?

Senator HARKIN. So the flu shot I got does not protect me from——

Dr. FAUCI. Not even a little bit. Not even a little bit. So—but don't worry because there's not H5N1 right here now. But we're concerned about it.

So what are we doing about it? The NIH component of the broader Department of Health and Human Services pandemic flu preparedness plan is the research limb. You know, the CDC does the surveillance, the identification, the public health measures. The FDA does the regulation of the vaccines and the drugs that we're screening for, and that's all done under the Office of Public Health Emergency Preparedness.

What we're doing is fundamental basic research on the virus, understanding its virulence and pathogenesis, getting sequence data on all of the various strains so that we can make them available to investigators to do things like screening for drugs, targeting for drugs, and the development of vaccines.

Probably the thing that's of most practical concern to you and the committee and the general public is that we have moved very rapidly in identifying the H5N1 using a particular molecular technique

developed by one of our grantees to develop a seed virus. Two weeks ago, we started the screening for a trial. Last week we gave the first injections, and as of yesterday, we have over 150 people enrolled in a phase 1 trial of H5N1 in three centers in our network of vaccine centers in Rochester, New York, UCLA, and Baylor, I believe.

We have now data that we're going to be collecting on the safety, what is the proper dose of the vaccine, and what is the difference in the immunogenicity in normal adults. That will be finished within a period of a couple of months, people from 18 to 64. Then we're going to move on to people greater than 65, and then we're going to do it in children.

In addition, finally, as part of the departmental program, we've purchased 2 million doses for the strategic national stockpile of H5N1 in anticipation of being able to scale this up in commercialized lots, not just thousands or millions, but tens of millions if we need it.

Finally, the Department's plan is to stockpile Tamiflu, which is the antiviral to which this particular virus is susceptible.

Senator HARKIN. What did you say?

Dr. FAUCI. Tamiflu. The regular name for it is Oseltamivir. It's an anti-influenza drug.

Senator HARKIN. I'm glad you've cleared that up for me.

TRAVEL RISKS ASSOCIATED WITH AVIAN INFLUENZA

Well, now, the only follow-up question I have is—okay, so we're not exposed to avian influenza, but they are in Southeast Asia. How concerned should we be of people traveling back and forth, picking up the virus, bringing it back here, and transmitting it?

Dr. FAUCI. At this point not. But the CDC, together with WHO, is heightening in a very accelerated way their surveillance mechanism in Southeast Asia. Since the virus does not transmit efficiently at all from human to human, it is extraordinarily unlikely that you would have a situation where someone would be infected, that most likely would be a chicken farmer, who would then get on a plane and come to Washington.

So the chance of that is extremely unlikely. For that reason, there are no public prohibitions on travel with regard to this.

I just want to mention one thing, I just thought of it. I gave you—just because I want the record to be correct—the other center that's doing the trial is not Baylor. It's the University of Maryland in Baltimore.

Senator HARKIN. Thanks very much, Dr. Fauci.

Dr. FAUCI. You're welcome.

HUMAN CANCER GENOME PROJECT

Senator HARKIN. Dr. von Eschenbach, I want to ask something Dr. Jim Watson brought up to me a couple of times, and that has to do with the human cancer genome project.

Dr. VON ESCHENBACH. Yes, sir.

Senator HARKIN. About the need for that kind of effort. I understand that NCI and the Human Genome Research Institute, Dr. Collins, have teamed up on an effort called the human cancer ge-

nome project. Just what is this? What are you doing? Tell me about this.

Dr. VON ESCHENBACH. Well, thank you, Senator, for the question, and also thank you very much for your passion and concern for patients, especially cancer patients. This effort is intended to address much of our opportunity in understanding cancer. We know, though it is a series of complex diseases, it is also a disease process. There is a portion of that process that defines our susceptibility to cancer and then the development and progression of that cancer to the point where it causes the suffering and death that we see all around us.

So we're trying to understand that cancer process. We're trying to understand it at the very fundamental genetic and molecular and cellular level as to why and how we're susceptible to different cancers, how and why they develop and then progress in some patients to the point that they actually take our life.

We have a series of investigations to understand that process. We're trying to understand it at the genetic level and also understand it at the molecular and proteomic level. We've even launched recently an effort in nanotechnology to begin to utilize that field to understand the process.

The specific project that you are referring to is one of those initiatives where we are teaming up with another NIH Agency, the National Human Genome Research Institute, to co-partner in an effort to understand and to determine all the genetic changes and mutations that determine our susceptibility to cancer and define the development of cancer.

We believe that if we understand those genes and those genetic changes, we'll be able to use that knowledge and that information to be able to select and screen patients to determine susceptibility, to be able to define the risk that one has for a particular type of cancer, so that we then have that knowledge and can use that to intervene earlier in a way to try to prevent that process from occurring. Also to be able to use the knowledge of those genetic changes so that we can find better methods to detect the development of cancer, because if we can pick up the development of those genetic changes and know that cancer is now starting in someone's body, we could then eliminate that cancer when it's still very early and do that much more safely and much more easily.

If we can detect and eliminate cancer early, we could eliminate the outcome of cancer, the suffering and death that we see. So this is one initiative that we believe holds great promise for achieving the goal of 2015, the elimination of suffering and death due to cancer.

Senator HARKIN. So you've embarked on this and——

Dr. VON ESCHENBACH. It's in process of development, sir. And we have a pilot project that we are in the midst of planning and developing so that we can create the infrastructure for a broader application of this.

Senator HARKIN. So when we meet again here later on, you'll be able to keep us updated as to what the progress of this is?

Dr. VON ESCHENBACH. Absolutely, sir.

Senator HARKIN. I appreciate that very much. I really don't have any more time. Did anybody else have any—Dr. Zerhouni, did you have anything else you wanted to add for the record?

Dr. ZERHOUNI. No. I really appreciate the questions you've posed today.

Senator HARKIN. Thank you. Again, I apologize for jumping on you on the conflict of interest, but I hope there's some people here from HHS, because that's really who I was directing it at.

But I'll say, we need you in forefront of this too. This is your NIH.

Dr. ZERHOUNI. I certainly am.

Senator HARKIN. I just don't think we can afford to continue to put this off. We've got to address it right away.

Dr. ZERHOUNI. I think you've heard me, sir.

Senator HARKIN. I know, and I appreciate that. Thank you all very much for the great job you do. Hopefully we can get that .5 up, but I don't know. We'll try our best.

Dr. ZERHOUNI. Thank you very much.

ADDITIONAL SUBMITTED STATEMENT

Senator HARKIN. Thank you all very much.

The subcommittee has received a statement from The National Alliance for eye and Vision Research which will be placed in the record.

[The statement follows:]

PREPARED STATEMENT OF THE NATIONAL ALLIANCE FOR EYE AND VISION RESEARCH

The National Alliance for Eye and Vision Research (NAEVR) is pleased to submit this written testimony to the file of the April 6, 2005, hearings of the Labor, Health and Human Services, Education and Related Agencies Subcommittee of the Senate Appropriations Committee.

ABOUT NAEVR

Founded in 1997, NAEVR is a non-profit advocacy organization comprised of 50 professional, consumer and industry organizations involved in eye and vision research. NAEVR's goal is to achieve the best vision for all Americans through advocacy and public education about the value and cost-effectiveness of eye and vision research sponsored by the National Institutes of Health (NIH), the National Eye Institute (NEI) and other federal research entities.

NAEVR REQUESTS FISCAL YEAR 2006 NIH FUNDING AT $30 BILLION TO MAINTAIN THE MOMENTUM OF DISCOVERY

Although NAEVR realizes that Congress faces an expanding set of challenges at home and abroad, we join the community of support for medical research in requesting Congress to fund the NIH at $30 billion in fiscal year 2006, or a 6 percent increase over the fiscal year 2005 level, to maintain the momentum of discovery. NAEVR believes that the NIH has made tremendous contributions that have served to improve the quality of lives for millions of Americans and contain healthcare costs.

NAEVR commends Chairman Specter's leadership in introducing Senate Amendment 173 to the fiscal year 2006 Senate Budget Resolution that would add $1.5 billion to the NIH beyond that proposed in the administration's budget, to a level of approximately $30 billion. NAEVR also recognizes the leadership demonstrated by the full Senate in successfully passing the amendment and Senate Budget Resolution, and we strongly urge the Senate and House conferees to maintain this number in the conference bill.

Congress' past bipartisan leadership in doubling the NIH budget from fiscal year 1998 to fiscal year 2003 has had a profound impact on the health care of all Americans, in terms of earlier, more accurate diagnosis of disease; more targeted, effective treatment options; more comprehensive, cost-effective prevention strategies; and the

transformation of acute diseases to chronic, manageable diseases. With this basis, NIH has plans to further transform how basic and clinical research is conducted through initiatives such as the *NIH Roadmap for Medical Research* (the NEI is a lead Institute on the Nanomedicine project) and *NIH Neuroscience Blueprint*, in which 15 Institutes are engaged, including the NEI.

NAEVR commends NIH Director Dr. Zerhouni for his leadership in eliminating roadblocks that prevent collaborative research and using NIH-directed dollars in a cost-effective manner. However, his efforts to maximize the return on medical research dollars can only go so far. For example, in the fiscal year 2006 funding process, NIH would need an increase of at least 3.5 percent just to keep pace with the Biomedical Research and Development Price Index (BRDPI). Since the fiscal year 2006 funding level in the administration's budget proposal would represent the third year in which the NIH would not keep pace with inflation, the gains realized from the past investment in the NIH will be jeopardized.

In summary, to ensure that NIH's momentum is not eroded further, and to continue the fight against diseases and disabilities that affect millions of Americans, NAEVR requests that Congress seek an NIH budget of at least $30 billion in fiscal year 2006.

NAEVR REQUESTS FISCAL YEAR 2006 NEI FUNDING AT $711 MILLION AS VISION HEALTH IS A "TOP PRIORITY" AMONG MANY PRIORITIES

NAEVR requests that Congress fund the NEI at $711 million in fiscal year 2006, or a 6 percent increase over fiscal year 2005. This "Citizens Budget" for the NEI represents the eye and vision research community's judgment as the level necessary to advance the breakthroughs resulting from NEI's basic and clinical research that will result in treatments and therapies to prevent eye disease and restore vision.

In presenting this request, NAEVR asks Congress to make this nation's vision health a "top priority" among the many priorities it faces in the fiscal year 2006 funding cycle for the following reasons:

—Eye and vision research responds to the nation's top public health challenges and touches the lives of all Americans.

—The eye is a unique biological system offering exceptional experimental advantages in which to conduct genetic, neuroscience and cellular mechanism research.

—Vision impairment and eye disease is a major public health problem that is growing and which disproportionately affects the aging and minority populations.

—The economic and societal costs of vision impairment and eye disease are significant and growing; adequately funding the NEI is a cost-effective investment in our nation's health.

—Past NEI-funded basic and translational research is resulting in treatments and therapies to slow the progression of vision loss and restore vision.

EYE AND VISION RESEARCH RESPONDS TO THE NATION'S TOP PUBLIC HEALTH CHALLENGES AND TOUCHES THE LIVES OF ALL AMERICANS

Dr. Zerhouni has identified the NIH's top public health challenges as an aging population; chronic diseases; health disparities; emerging diseases (primarily co-morbidities); and biodefense. NEI is responding to all of these challenges as they relate to eye and vision research:

—Not only has the NEI sponsored studies to characterize the incidence of age-related eye diseases such as age-related macular degeneration (AMD), glaucoma, diabetic retinopathy and cataracts, it sponsors extensive research into the cause and potential prevention of and treatments for these chronic diseases.

—Working with the National Center on Minority Health and Health Disparities (NCMHD), the NEI has sponsored studies to characterize vision impairment and eye disease disparities to direct further research—whether into the underlying physiological cause and potential concomitant therapy, or to the socio-economic or access issues that may enable it to focus its public health education programs.

—NEI has taken its basic research on diabetic retinopathy, a co-morbidity of diabetes, and tested treatments through a Clinical Trials Network. This optimal example of translating basic research "from bench to bedside" has resulted in treatments that are more than 95 percent effective and save the United States $1.6 billion annually.

—Going beyond the traditional focus on battlefield visual acuity, NEI's biodefense research has resulted in new therapies to treat infectious eye diseases and promote corneal healing.

While addressing the nation's top public health challenges, NEI research also touches all Americans, whether directly or through loved ones. NEI research has the potential to ensure the best vision health of individuals at all stages of life—from newborns to the most elderly?thereby ensuring their independence, productivity and quality of life.

THE EYE IS A UNIQUE BIOLOGICAL SYSTEM OFFERING EXCEPTIONAL EXPERIMENTAL ADVANTAGES IN WHICH TO CONDUCT GENETIC, NEUROSCIENCE AND CELLULAR MECHANISM RESEARCH

As the entire medical research community gains a better understanding of the genetic basis of disease, the eye emerges as a unique biological system in which to study cellular mechanisms and pathways. The eye and vision community is at the forefront of genetic research, as the eye offers accessibility and a system in which one can measure the potential effect from a treatment. For example, NEI-sponsored researchers have recently announced the discovery of a gene strongly associated with a person's risk of developing AMD, which is the leading cause of vision loss in older Americans. This may enable researchers to develop tests for the disease before symptoms begin to appear and when drug therapies might help slow its progress.

Since the retina is a direct outgrowth of the brain and nerve cells underlie the ability to process vision, the eye also serves as an important system in which to study neurodegenerative diseases. For example, NEI-funded researchers have recently announced the regeneration of the optic nerve in mice, which could potentially result in treatments for Americans blinded by glaucoma or other injuries that destroy the optic nerve, as well as for other Central Nervous System disorders.

VISION IMPAIRMENT AND EYE DISEASE IS A MAJOR PUBLIC HEALTH PROBLEM THAT DISPROPORTIONATELY AFFECTS THE AGING AND MINORITY POPULATIONS

Over the past 40 years, Americans have consistently identified fear of vision loss as second only to fear of cancer in public opinion polls. In recent NEI-sponsored research, patients with advanced AMD equated that condition to the gravest chronic diseases. These societal implications of vision impairment and eye disease are important since, as of the year 2000 census, there were more than 119 million Americans age 40+ who are most at risk from age-related eye disease such as AMD, glaucoma, diabetic retinopathy and cataracts.

In 2004, an NEI-sponsored study reported that vision loss from eye diseases will increase as Americans age. Also in 2004, the NEI reported on an African American subset analysis in its Ocular Hypertension Treatment Study (OHTS) and initial findings from its Los Angeles Latino Eye Study (LALES), both of which were cosponsored by the NCMHD. Combined, these three studies reported that:

—Blindness or low vision currently affects 3.3 million Americans age 40+, or 1 in 28, and is projected to reach 5.5 million by year 2020.

—Age-related eye diseases currently affect more than 35 million Americans age 40+, and include intermediate-to-advanced AMD, glaucoma, diabetic retinopathy and cataracts. This number is projected to increase to about 50 million by the year 2020.

—More than 1.8 million Americans currently have advanced AMD, and this number is expected to grow to 3 million by the year 2020. Another 7.3 million Americans currently have intermediate-stage AMD. Currently, 200,000 Americans each year develop advanced AMD, and this number is expected to double by 2020. Because AMD affects the part of the eye called the macula, which is necessary for central vision, it affects a person's ability to read and drive. This has an enormous impact on quality of life and independence for older Americans.

—Glaucoma, a chronic potentially blinding disease that requires life-long treatment to control it, currently affects 2.2 million Americans, with 3.3 million expected to develop it by the year 2020. Glaucoma is now the leading cause of blindness in the fast-growing Hispanic population age 65+. Glaucoma is almost three times as common in African Americans as in White Americans and is the leading cause of blindness in the African American population.

—Diabetic retinopathy is the leading cause of blindness in the industrialized world in people between ages 25 and 74. It currently affects 4.1 million Americans age 40+, or one out of 12 Americans with diabetes in that age group, and is expected to increase to 7.2 million by the year 2020. Although successfully treatable in more than 95 percent of cases, many people do not know they are diabetic until symptoms, such as vision loss, occur. And with estimates of 50 million Americans having diabetes by the year 2020 at a yearly cost of $1 trillion, and one-third of all American children born in year 2000 developing it in

their lifetimes, there will be increasing demand for research into new treatments and prevention therapies.

—Cataracts, which are the leading cause of low vision, currently affect nearly 20.5 million Americans age 65+, which is projected to increase to 30.1 million Americans by the year 2020. In the United States, a cataract is widely treatable by removing the natural lens and implanting an intraocular lens (IOL). However, in the rest of the world, cataracts are the leading cause of blindness due to lack of access to adequate care.

The past investment in the NEI's basic research has yielded breakthrough discoveries in the potential cellular mechanisms that result in these diseases, and its clinical research has resulted in an array of treatments for these conditions. However, the expanding population at risk for eye and vision disease will demand new and more effective therapies that restore vision or ultimately prevent the onset of these diseases. Adequately funding the NEI now ensures that its basic and clinical research "in the pipeline" comes to fruition and can be responsive to this growing public health problem.

THE ECONOMIC AND SOCIETAL COSTS OF VISION IMPAIRMENT AND EYE DISEASE ARE SIGNIFICANT; FUNDING NEI IS A COST-EFFECTIVE INVESTMENT

Although the NEI estimates that the current annual cost of vision impairment and eye disease to the United States is $68 billion, this number does not fully quantify the impact of lost productivity and diminished quality of life. And as noted above, this financial burden to both the public and private sector is expected to increase dramatically, primarily due to an aging population and the growing prevalence of eye diseases that result in vision loss.

Adequately funding the NEI can delay, save and prevent expenditures, especially those associated with the Medicare and Medicaid programs, and is, therefore, a cost-effective investment. For example:

—As previously cited, the NEI-sponsored Early Treatment Diabetic Retinopathy and Diabetic Retinopathy studies have saved as much as $1.6 billion per year in costs of blindness and vision impairment and resulted in treatments that are more than 95 percent effective.

—NEI-funded researchers have developed treatments for Retinopathy of Prematurity (ROP), a blinding complication in premature babies. As a result, more than 1,500 infants born this year with the most serious form of this condition can experience sighted lives, which would have cost the government $1 million in benefits and lost taxes over the lifetime of each child.

—Economists estimate that cataract surgery provided Americans over $300 billion in benefits in 2003 alone.

Funding the NEI at $711 million in fiscal year 2006 is a cost-effective investment, as it will directly save healthcare expenses and return individuals to productive roles in society.

PAST NEI-FUNDED RESEARCH IS RESULTING IN TREATMENTS AND THERAPIES TO SLOW THE PROGRESSION OF VISION LOSS AND RESTORE VISION

The NEI has an impressive record of accomplishment over the past 5 years, as documented in its *National Plan for Eye and Vision Research*. Some of the most exciting developments that have widespread implications for Americans of all ages and races include:

—NEI is conducting additional clinical trials on nutritional supplements that may slow the progression of AMD, following previous research demonstrating that zinc and three antioxidant vitamins are effective in reducing vision loss in people at high risk for developing advanced AMD.

—An NEI-sponsored study has found that eye injections of bone-marrow derived stem cells prevented vision loss in two rodent models of Retinitis Pigmentosa (RP), a family of eye diseases that cause vision loss. This study raises the possibility that patients could receive an injection of their own bone marrow stem cells to preserve central vision.

—NEI-supported investigators are moving closer to human clinical trials of a gene therapy to treat neurodegenerative eye diseases, including Leber Congenital Amaurosis (LCA), which is a rapid retinal degeneration that blinds infants in the first year of life. Previous research has restored vision in dogs with LCA. This gene therapy not only has direct implications for the 9 million Americans affected by AMD, RP, Usher Syndrome and the entire spectrum of retinal degenerative diseases, but can potentially lead to therapies for glaucoma, diabetic retinopathy and cataracts.

CONCLUSION

NAEVR supports fiscal year 2006 NIH funding at $30 billion to ensure that our nation's medical research infrastructure can maintain its momentum of discovery. NAEVR also requests that Congress make our nation's vision health a "top priority" among many priorities by funding the NEI at $711 million in fiscal year 2006. NEI-funded research results in therapies that reduce health expenses and return individuals to productive lives. It is a cost-effective investment in maintaining the momentum of discovery and vision health for all Americans.

ADDITIONAL COMMITTEE QUESTIONS

Senator HARKIN. There will be some additional questions which will be submitted for your response in the record.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing.]

QUESTIONS SUBMITTED BY SENATOR ARLEN SPECTER

OBESITY RESEARCH

Questions. Last year, NIH announced release of a comprehensive Strategic Plan for Obesity Research. What initiatives have you undertaken, particularly to address the critical problem of childhood obesity, since release of this plan?

Answer. The NIH is pursuing a broad spectrum of research avenues consistent with the recommendations in the Strategic Plan for NIH Obesity Research. An important area of focus of these efforts is childhood obesity, to address the serious impact obesity has on children—potentially leading to a lifetime of serious health problems. Highlights of such efforts include fostering new research on prevention and treatment of pediatric obesity in primary care settings and other site-specific settings, which may include the home, day-care, school, or other community venues. In another effort, the NIH is beginning a project to develop a rating system for youth obesity-related policies. The current effort involves developing, for use as a research resource, a system to rate factors associated with physical activity and nutrition that are addressed by such policies. Such factors may include, for example, aspects of physical education or recess in schools. Once developed, this research resource would then be made available to investigators as a tool to facilitate analysis of the relative impacts of these factors on behaviors relevant to obesity. This effort would encompass policies at both the state and local levels. In developing this research resource, the NIH is coordinating with the CDC and other organizations which are supporting related efforts.

Other recently-launched NIH research would impact obesity in both adults and children. For example, the NIH is encouraging new studies to address the influence on obesity of factors in the "built environment," such as aspects of community design that may hinder physical activity. An upcoming conference will focus on environmental factors and obesity in youth. Improved technologies would facilitate a wide range of investigations. Such improved technologies would encompass, for example, the areas of more accurately measuring calorie consumption (energy intake) and physical activity (energy expenditure), and monitoring whether a person's energy intake and expenditure match (a state of energy balance) or whether one is greater. Thus, the NIH released research solicitations to bring innovative bioengineering technology to address issues in energy balance, intake, and expenditure. Capitalizing on major ongoing NIH research investments, the NIH is continuing to solicit proposals for ancillary studies to several existing obesity-related clinical trials and networks; the NIH is also encouraging other productive partnerships between basic and clinical researchers. Interdisciplinary research focused on obesity is also being enhanced as a result of a recent NIH Roadmap initiative to support new Exploratory Centers for Interdisciplinary Research; several of these centers will focus on obesity. The NIH is also continuing to pursue genetic studies of obesity. Efforts are underway to develop an Intramural Obesity Clinical Research Center, on the NIH campus, to generate new knowledge regarding the prevention, treatment, and underlying molecular mechanisms of obesity and its associated diseases. Intramural-extramural collaboration will be a focus of these efforts.

Examples of efforts currently being developed include a new initiative to study how factors such as maternal weight during pregnancy can lead to obesity in offspring. Another effort is being planned to support collaborative research on the neurobiological basis of human eating behavior, bridging the gap between under-

standing at the genetic and molecular level of neural pathways involved in food intake and the understanding of behavioral influences on human obesity.

INFLUENZA

Question. Dr. Fauci, why is the spread of avian influenza so alarming?

Answer. The spread of avian influenza is of great concern because in the past, highly virulent pandemic influenza strains have originated as avian influenza. Influenza pandemics are global outbreaks that emerge infrequently and unpredictably and involve strains of virus to which humans have little or no immunity. Three deadly influenza pandemics have occurred in the 20th century: in 1918, 1957, and 1968. The 1918–1919 pandemic was by far the most severe, killing approximately 500,000 people in the United States and 20–40 million people worldwide—almost two percent of the global population at that time. Worldwide, the pandemics that began in 1957 and 1968 killed approximately 2 million and 700,000 people, respectively.

H9N2 and H5N1 influenza are two avian viruses that have jumped directly from birds to humans and have significant pandemic potential. In 1999 and 2003, H9N2 influenza caused illness in three people in Hong Kong and in five individuals elsewhere in China; fortunately, the virus did not acquire the ability to spread from human to human. Between January 28, 2004 and April 14, 2005, there were 88 confirmed cases of and 51 deaths from H5N1 avian influenza infection in humans in Cambodia, Thailand, and Vietnam, according to the World Health Organization. To date, there have been a small number of cases where human-to-human transmission of the virus may have occurred. However, public health experts fear that the longer and more widely the H5N1 virus circulates in poultry, the greater the likelihood that the virus may evolve into one that is more easily transmitted between people. If this were to happen, a worldwide pandemic could follow.

Question. What steps is your Institute taking to address this issue?

Answer. The National Institute of Allergy and Infectious Diseases (NIAID) is using a multi-faceted approach to address the threat of avian influenza, including surveillance of animals, vaccine and antiviral development, basic research, and genome sequencing. Through a contract to St. Jude Children's Research Hospital, NIAID is supporting disease surveillance in wild birds, live bird markets, and pigs in Hong Kong, allowing scientists to track potential emergent influenza strains. In January 2005, the contract was expanded to include animal surveillance in Vietnam, Thailand, and Indonesia.

The Institute has taken a number of steps to develop and clinically test vaccines against the two influenza viruses with the greatest pandemic potential. For example, under contract to NIAID, Chiron produced 40,000 doses of an H9N2 inactivated vaccine; a Phase I clinical trial of this vaccine in healthy adults began March 31, 2005. NIAID intramural scientists have also developed an attenuated H9N2 vaccine candidate that will soon be evaluated in humans.

NIAID has also initiated clinical testing of an H5N1 influenza candidate vaccine developed by NIAID-supported researchers at St. Jude Children's Research Hospital. In January 2004, these researchers obtained a clinical isolate of the highly virulent H5N1 virus that was fatal to humans in Vietnam in late 2003 and early 2004. They used a new technique called reverse genetics to create an H5N1 candidate vaccine from this strain. In May 2004, NIAID awarded contracts to Sanofi (formerly Aventis) Pasteur and Chiron for the manufacturing and production of inactivated vaccine against H5N1 influenza using this strain. Sanofi Pasteur delivered vaccine to NIAID in early March 2005; delivery of the Chiron vaccine is estimated to be in fall 2005. NIAID's Vaccine and Treatment Evaluation Units (VTEUs) currently are conducting a clinical trial of the Sanofi Pasteur vaccine in healthy adults. Following the review of the safety and immunogenicity data from the adult trial, NIAID plans to initiate trials of the H5N1 vaccine in healthy elderly and other populations. In addition, NIAID intramural researchers have developed three attenuated H5N1 vaccine candidates, which have been shown to be protective in mice; initial clinical trials of one of these vaccine candidates may begin as early as this year.

Efforts also are underway to test and improve antiviral drugs to prevent or treat avian influenza. NIAID is supporting an animal study to determine if combination therapy with two classes of antiviral drugs—neuraminidase inhibitors and adamantanes—is more effective that a single antiviral in reducing viral replication and emergence of drug resistant strains. The Institute is also supporting the development and testing of a long-acting next generation neuraminidase inhibitor that can be administered once per week.

NIAID supports a number of basic research projects that could lead to significant advances in pandemic influenza preparedness, including research that could lead to

vaccine strategies that would provide broader protection against a wide range of influenza strains and strategies to allow rapid production of a vaccine against a newly emergent strain. In addition, the Influenza Genome Sequencing Project, launched in the fall of 2004, is a collaboration between NIAID, the Centers for Disease Control and Prevention (CDC) and other organizations. The complete genetic sequences of thousands of influenza virus isolates will be determined and made available to the scientific community; to date, approximately 120 viruses have been sequenced. This program will enable scientists to better understand the emergence of influenza epidemics and pandemics by observing how influenza viruses evolve as they spread through the population. Moreover, scientists will be able to match viral genetic characteristics with virulence, ease of transmissibility, and other properties; this knowledge could lead to improved methods of treatment and prevention, as well as guide the public health emergency response should an influenza pandemic emerge.

BIOTERROR THREATS

Question. Dr. Fauci, please update us on the progress in the development of countermeasures against bioterror threats?

Answer. Since the attacks of September 11, 2001, and the anthrax attacks the following month, the United States has made significant progress in developing countermeasures against bioterror threats. The National Institute of Allergy and Infectious Diseases (NIAID) supports a comprehensive biodefense research and development program, which includes the development of biodefense countermeasures to combat Categories A, B, and C biological agents, as well as the expansion of the national research infrastructure and resources available to biodefense researchers. Basic research on microbes and host immune defenses serves as the foundation for applied research to develop the vaccines, therapeutics and diagnostics that the United States will need in the event of a bioterror attack.

The NIAID biodefense program has benefited from the passage of the Project BioShield Act of 2004, which granted the National Institutes of Health and NIAID authorities to expedite and simplify the solicitation, review, and award of grants and contracts for the development of critical medical countermeasures. NIAID used its new BioShield authorities to make recent grant awards for research aimed at the development of therapeutics for botulinum toxin, Ebola virus, anthrax, pneumonic plague, tularemia, and smallpox. Using BioShield authorities, the standard eighteen-month timeline from the conception of an initiative to grant award was reduced to approximately nine months. In fiscal year 2005, the Institute anticipates making additional awards using these BioShield authorities for research related to the protection of the immune system against damage by radiological or nuclear attacks.

The following are a few specific examples of NIAID's progress in the research and development of biomedical countermeasures against Category A bioterror agents:

Anthrax

In 2002 and 2003, NIAID initiated early and advanced product development and testing of the next-generation anthrax vaccine (rPA) by awarding contracts to two companies, Avecia and VaxGen. In November 2004, DHHS used its own Project BioShield authorities to award a contract to VaxGen to supply 75 million doses of rPA anthrax vaccine to the SNS. In addition, NIAID-supported scientists are conducting research to identify new targets for therapeutics. Scientists supported by NIAID determined the structure of the anthrax toxin, providing a better understanding of how the toxin causes disease and giving scientists the opportunity to design drugs that will specifically inhibit the anthrax toxin.

Smallpox

In 2003, NIAID initiated the advanced development of Modified Vaccinia Ankara (MVA) smallpox vaccine through contracts to Acambis and Bavarian Nordic. Contracts awarded in October 2004 are supporting larger scale manufacturing of the MVA vaccine as well as additional studies of safety and effectiveness in animals and humans. Though a vaccine is the only proven way to prevent smallpox infection, therapeutics to fight an infection are also an important component of the biodefense arsenal. NIAID-supported scientists have discovered a new way to block the ability of smallpox to spread from cell to cell, which may lead to the development of next-generation antiviral drugs to combat smallpox and other viral infections.

Plague

NIAID is supporting the manufacture of a plague vaccine through a contract awarded to Avecia in October 2004; this award will also support preclinical testing in animals and initial human clinical trials.

Tularemia

In collaboration with the Department of Defense (DOD), NIAID is conducting a Phase I clinical trial using the DOD's Live Vaccine Strain (LVS) tularemia vaccine. In October 2004, NIAID modified an existing contract with DynPort Vaccine Company to support the manufacture of additional LVS vaccine in anticipation of possible future clinical trials as well as for use in evaluation of the stability of the vaccine.

Botulinum toxin

In March 2005, NIAID made its first contract award using Project BioShield authorities to XOMA LLC, for the production of botulinum toxin monoclonal antibodies (serotype A) for clinical evaluation. In fiscal year 2005, NIAID expects to use Project BioShield authorities to make an additional contract award for the production of a recombinant botulinum toxin vaccine (serotype E) for clinical evaluation.

Viral hemorrhagic fevers

NIAID's Vaccine Research Center (VRC) is currently conducting the first human trial of a vaccine to prevent Ebola infection. In addition, NIAID grantees and scientists recently made a critical discovery related to how Ebola virus infects cells. These findings raise the possibility that a broad-spectrum antiviral therapeutic could be effective against multiple hemorrhagic fever viruses such as Ebola and Marburg.

BIODEFENSE FUNDING

Question. Dr. Fauci, we have heard that members of the scientific community have criticized that increased biodefense funding at NIH has come at the expense of other important public health research. Can you comment on this?

Answer. The terrorist attacks of September 11, 2001, and the dissemination of anthrax spores through the U.S. mail later that fall prompted the Administration, with bipartisan support from Congress, to dramatically increase spending on biodefense research, with the specific goal of developing medical countermeasures to protect the public against agents of bioterror. More than $1.5 billion was added to the National Institutes of Health (NIH) budget in fiscal year 2003 for biodefense research. These funds are additive to funds for other infectious diseases research; the biodefense funds did not and will not divert resources from other important infectious diseases research.

The non-biodefense resources of the National Institute of Allergy and Infectious Diseases (NIAID) increased by more than 50 percent from fiscal year 2000 to fiscal year 2005, keeping pace with or exceeding the average annual increases received by NIH during this same period.

DEVELOPING ADVANCED TECHNOLOGIES

Question. From everything being written in the media, there is reason to be optimistic that we are close to unraveling the mysteries of cancer. Much of the progress being made is a direct result of new technology that wasn't available even only a few years ago. If there are still gaps in available technology that are preventing researchers from having a complete understanding of the complexities of cancer, has NCI considered ways in which the necessary tools could be developed?

Answer. Research over the past three decades has led to unimagined progress in our understanding of the cancer process at the genetic, molecular, and cellular levels. The combination of scientific talent, infrastructure, partnerships, and expertise coupled with an extraordinary array of advanced technologies is allowing us to understand cancer as a process—a process that begins with a single genetic alteration and proceeds through several stages to a lethal disease. Even now, as we stand an inflection point for progress in eliminating the suffering and death due to cancer, emerging technologies hold the key to accelerating our understanding of the complexities of cancer and how to prevent, diagnose, and treat cancer in its many forms. As we search for the most effective ways to harness the power of scientific discovery and to enhance our understanding of cancer's complexities, we know that the most direct path will be through the optimal integration of science and technology, specifically advanced technologies such as bioinformatics, cancer imaging, proteomics (the study of proteins), and nanotechnology (man-made devices minuscule enough to enter living cells).

The National Cancer Institute (NCI) has already taken steps to achieve paradigm shifting technology advances through the launch of the cancer Bioinformatics Grid (caBIG), an unprecedented platform to be available to the entire cancer research community. NCI has also established the Alliance for Nanotechnology in Cancer to

unite a broad array of programs to maximize the technology outputs. Initiatives in proteomics and cancer imaging are underway as well. As these technologies mature, we must also create the technology development resources and the seamless system needed to capitalize on their discoveries.

PERSONALIZED MEDICINE

Question. Over the past year, there has been a great deal of discussion surrounding research areas such as genomics, proteomics, and metabolomics. Articles suggest that research in these areas will provide research breakthroughs that will translate into new forms of targeted therapies and a way to personalize the treatment that cancer patients will receive in the future. Is this a realistic expectation or just science fiction?

Answer. Personalized medicine is not only a real possibility; it is critical to achieving NCI's goal to eliminate the suffering and death due to cancer by 2015. The Nation's investment in cancer research has led us to a point today where we're beginning to understand cancers at the molecular and genetic and cellular levels, and this understanding is influencing our selection of therapy and moving us to personalize medicine and personalize oncology. As our understanding of the cancer process increases, so does our ability to seek out and target key points in that process to disrupt and reverse the development of cancer. Part of our challenge is to understand how those targets differ from cancer type to cancer type and how each patient might react differently to potential therapies. Technologies such as molecular and genetic profiling and proteomics are opening the door to understanding these diseases and how they behave on an individual basis.

Using molecular profiling, NCI scientists have been able to identify and predict mantle cell lymphoma patients' survival following diagnosis based on the each cancer's distinct signature. Knowing whose disease is slow-moving and whose is progressing rapidly should help determine who would do well with a watchful waiting approach and who may benefit from early and aggressive treatment, possibly with new therapeutic regimens. For chronic lymphocytic leukemia, scientists have known for several years that there were two types of this leukemia, but the means for telling the two apart and affecting treatment choices was complex and not available to most patients. The same NCI group recently showed that expression of a single gene, ZAP–70, is a surrogate for this distinction, paving the way for better treatment choices for more patients.

Recent breakthroughs are also enabling scientists to identify patterns of protein markers associated with cancer initiation and progression and with particular cancers. Biomarkers (tumor indicators found in body fluids or tissues) hold promise for making personalized medicine a reality. They have many potential applications including early diagnostic testing, monitoring response to treatment, detecting metastatic disease, and building "designer" therapies. Already, information-rich blood sample proteins are being use to detect patients with ovarian cancer, effectively differentiating early-stage cancer patients from unaffected individuals. Similar methods potentially may be used to monitor a patient's response to molecularly targeted drugs, which could prove useful in designing patient-tailored therapies.

CANCER BIOMEDICAL INFORMATICS GRID

Question. NCI has built an impressive network of cancer centers around the country. Have you developed any resources that would enable the cancer centers and the broader cancer research community to share data and information?

Answer. By using the power of modern information technology, NCI is leading the way in developing a bioinformatics platform that promises to revolutionize the biomedical research enterprise. Scientists in various disciplines will have access to a common infrastructure for collaboration and integration of findings, and new "plug and play" tools developed by the researcher community will make it possible for investigators to greatly accelerate their research. For example, researchers at Cancer Centers across the country will be able to access data on the molecular characteristics of patients with a particular type of cancer who are being treated with a specific drug. Diverse data mounted on common platforms will permit researchers to use innovative analytic tools to mine the information in ways inconceivable a few years ago.

Up to the present, bioinformatics resources have been developed in organizational isolation, with tremendous variability in rules, processes, vocabularies, data content, and analytical tools. NCI will address these concerns and strengthen the potential for bioinformatics integration with the cancer Biomedical Informatics Grid (caBIG). The caBIG will provide a unifying architecture to transparently connect information and tools much like a home entertainment system in which components are made

by different manufacturers but built to common standards that allow users to combine them in various ways. Our long-term goal for bioinformatics is to improve the sophistication of information technology use and surmount the barriers that limit interaction across research institutions. NCI is currently piloting a core infrastructure with the participation of 50 Cancer Centers.

We are also fostering the development and use of new informatics technology to accelerate, better coordinate, and facilitate participation in NCI-supported clinical research. Currently, volumes of valuable raw data are not tapped, effective best practices are not widely distributed, and resources are wasted because of duplication of effort. With new bioinformatics tools and infrastructure, trials will be completed more quickly in multi-institutional settings with uniform electronic case report forms and data reporting systems. Databases and analytical tools will make information from all clinical trials available to NCI-supported researchers for efficient patient accrual, information retrieval, and data analysis. Informatics systems will assist the cancer community with priority setting and allow for fuller participation and a more transparent decision making process. Advocacy groups and individual patients will be empowered to participate in clinical research and to authorize use of materials for basic science investigations. Confidential clinical and proprietary information will be protected by controlled, secure access. Just as e-business models have transformed the American market place, the caBIG platform will overcome traditional institutional limitations. Community practitioners, clinical research organizations, and academic centers will be linked through this new model of clinical research. Healthcare providers will become full partners in the research enterprise and educated consumers of research findings.

CANCER SURVIVORSHIP

Question. Recent statistics show that there are now nearly 10 million cancer survivors in the United States. This is a dramatic change from the outcome that the majority of people diagnosed with cancer faced in the not too distant past. What have been the key advances in medicine that have provided so many more people with a healthy outcome after being diagnosed with cancer?

Answer. Healthy outcomes for cancer can be primarily attributed to two key areas—early detection and prevention, and better treatment regimens. Newly aligned goals focused on preventing cancer from occurring and detecting it early when it is most curable are the keys to reducing the incidence of cancer. Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer have given us more effective ways to prevent the disease. New evidence-based interventions encourage lifestyle improvements in diet and physical activity, discourage smoking, and promote the use of safe and fully tested chemoprevention approaches for people at risk. Pioneering proteomic and biomarker advances and the promise of nanotechnology give hope for the early detection and diagnosis of cancer and prediction of patient response to treatment. Advanced information systems and methods of evaluation maximize the impact of existing technologies. NCI is ramping up specimen repositories and widely accessible bioinformatics resources to support the development of these breakthroughs.

Newer and better drugs are being developed every day, and combinations of many of these drugs are leading to longer survival times for many cancer patients. For example, the long-term outlook for breast cancer survivors improved significantly with news of a study that revealed the benefits of a drug that inhibits the synthesis of the hormone estrogen. The large, international study of the drug letrozole was specific to postmenopausal women who had been treated for early stage breast cancer that was estrogen-receptor positive and had just completed a five-year course of tamoxifen. Women who took letrozole (Femara®) were 43 percent less likely to experience a recurrence compared to women who took a placebo. The study, begun in 1998, was stopped ahead of schedule in 2003 when the positive effects became clear so that the women taking a placebo could be offered the drug.

Another example is the promising agent, iodine-131 tositumomab (Bexxar®), which is easier to take and less toxic than standard chemotherapy and has significant impact in extending the lives of patients who took it. In a phase II trial that included 76 patients with advanced-stage follicular lymphoma, nearly all of the patients (95 percent) responded to treatment, and three out of four were free of the disease after a single course of treatment. Five years later, most of the patients were in remission.

CANCER PREVENTION

Question. The development of new ways to treat cancer seems to be highlighted in the press quite often. It makes more sense to find ways to prevent cancer—can you tell us about any progress NCI has made in cancer prevention?

Answer. The prevention of cancer focuses on studying and modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting the carcinogenesis process through early medical intervention. We can save many lives, for example, by continuing to advance understanding of the biological and behavioral basis of nicotine addiction and energy balance. Evidence from recent NCI-sponsored studies suggest specific gene variations can affect smokers' cravings and that bupropion, an antidepressant used to help smokers quit, may ease these cravings, especially in women. Other medications to help smokers quit are under development and current evidence suggests that information and referrals from quit lines, as well as behavioral counseling from healthcare providers, significantly increase abstinence rates.

NCI is also supporting the development of prevention vaccines and chemopreventive agents for suppressing the carcinogenic process either at its inception or in pre-invasive stages. A new vaccine that targets the infectious agent human papilloma virus (HPV), implicated in cervical cancer, is being tested in clinical trials and is anticipated to be available to women at risk in the near term. Preclinical studies are beginning to identify prevention agents that impact cellular level targets to intervene in the cancer process, and clinical trials will test the value of these agents in preventing disease. NCI has established a new consortium of research centers to conduct early phase cancer prevention clinical trials. In 2004, NCI completed recruitment of 19,747 postmenopausal women at increased risk of breast cancer to participate in a clinical trial of the chemopreventive agent Raloxifene. Another prevention trial, the Prostate Cancer Prevention Trial, ended early after showing that men who took finasteride reduced their chances of getting prostate cancer by nearly 25 percent compared to men taking a placebo. A new proteomics technique has been used to successfully distinguish people who responded well to a drug that reduces colon polyps from those who did not. This technique increases our ability to target preventive agents to those who will most benefit. The impact preventative medicine and behavioral research have on reducing the cancer burden will continue to grow as similar techniques are developed and refined.

As we make such breakthroughs, we must actively translate prevention research into improved outcomes and facilitate the role of public policy to see that all people have knowledge of and access to preventive medicine and approaches. NCI understands that the media are a critical component of health communication as it relates to cancer prevention and we are working to optimize dissemination to patients, caregivers, and at-risk populations. For example, inadequate nutrition and physical activity appear to contribute to a sizable proportion of cancers. Through NCI's 5 A Day for Better Health Program, we seek to increase public awareness of the importance of eating 5 to 9 servings of fruits and vegetables every day for better health and provide consumers with specific information about how to include more servings of fruits and vegetables into their daily routines. NCI has also established Centers of Excellence in Cancer Communication Research, two of which are examining how the media communicate about cancer prevention. Through efforts like these, NCI is seeking ways to better work within media constructs to raise the level of dissemination and understanding of evidence-based cancer prevention messages.

CLINICAL RESEARCH AND ACADEMIC HEALTH CENTERS

Question. Dr Zerhouni, as a result of the recent doubling of NIH by Congress we've seen a remarkable increase in fundamental knowledge about diseases like Alzheimer's, Parkinson's and diabetes. But I'm sure you understand that knowledge, in and of itself, is not enough unless it's put to use. Many of us are concerned that the next step in the process—the clinical research that translates into cures and improved treatments—isn't getting enough attention. Please tell us specifically what's being done to get science from the bench to the bedside, and whether you have enough legislative authority to put more emphasis on that side of the equation?

Answer. In order to improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin with a clinical observation in a single patient or group of patients, or at "the bench" with basic research—in which scientists study disease at a molecular or cellular level. However, the discovery must then be translated to the clinical level, or the patient's "bedside." Translation is complicated, with input needed from a multidisciplinary team of scientists and other professionals.

In recent years, NIH-supported studies have addressed important translational issues, which have had direct implications for patient care on the front lines of medicine. The Women's Health Initiative assessed whether hormone replacement therapy (HRT) in post-menopausal women reduced heart attack rates; results demonstrated that it did not, and in fact, increased health risks; the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the occurrence of heart attack and stroke in high-risk hypertensive patients treated with either newer classes of drugs or with long established, inexpensive diuretics, and found that the diuretics were at least as effective as the new, more expensive medications; the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) tested whether an implantable cardiac defibrillator (ICD) or an antiarrythmic drug would help prevent sudden death in heart failure patients, and reported that the ICD significantly reduced deaths (while the drug was no better than placebo); the National Emphysema Treatment Trial (NETT) tested the effectiveness of bilateral lung volume reduction surgery (LVRS) in the treatment of emphysema, and established that that LVRS benefits some but is harmful to others. Results were used as the basis for CMS coverage decisions regarding LVRS.

Despite these and other important findings, NIH recognizes that concerns have been raised about the status of clinical and translational research. The agency is accelerating and strengthening this focus through the "Re-engineering the Clinical Research Enterprise" initiative, which is part of the NIH Roadmap. By integrating clinical and translational resources—such as informatics, biostatistics, career development, regulatory support—into a unified program, the NIH aims to greatly enhance the efficiency and scope of clinical research. This will allow more rapid translation of basic research into studies that can be performed in human subjects and provide tools for the rapid and broad dissemination of the results of clinical trials.

As a result of Roadmap initiatives, academic institutions are beginning to undergo transformative changes to break down organizational roadblocks and disciplinary silos and bring individuals with different types of expertise into newly collaborative, integrative structures focused on solving complex health problems. There are also experiments underway that will allow for the creation of enhanced training and career pathways for individuals in the translational and clinical sciences. Because there is broad heterogeneity among the individual cultures of the AHCs, NIH is encouraging flexibility in experimenting with different and innovative approaches to address the need for training the clinical and translational investigators of the 21st century.

Moreover, the NIH Clinical Roadmap is working to develop a cadre of community-based physicians trained to carry out clinical studies in the context of their own health care settings, and to be leaders in translating cutting edge research findings directly into clinical care. An ongoing study is evaluating the feasibility and mechanisms necessary to succeed in implementing such a program.

Also under the aegis of the Roadmap, the NIH has established a new Clinical Research Policy Analysis and Coordination Program to stimulate the development of coordinated policies, practices, and tools to harmonize Federal regulatory policy and to ensure efficient oversight of clinical and translational research and of human subject protections.

In addition, NIH is fostering intergovernmental relationships with the Centers for Medicare and Medicaid Services (CMS), the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC) and other agencies and health care plans to help ensure that clinical research results are used to develop evidence-based, cost-effective healthcare.

In its efforts to address the bottlenecks in translating results from clinical research into improved treatments and other interventions, the NIH aims to create a coordinated and supportive new infrastructure that will facilitate the more rapid translation of discoveries from the laboratory to the healthcare setting.

Question. On a related note, the academic health centers where clinical research is carried out—like Case Western Reserve, for example—are being squeezed. Part of the problem is the result of unfunded federal mandates like HIPAA. How does this affect NIH's ability to support clinical research, and ultimately help patients?

Answer. NIH recognizes the many requirements to which institutions must respond as they conduct and oversee clinical research. While these requirements pertain to important matters like human subject protections and safety oversight, NIH believes that much can be done to streamline them, thereby enhancing their effectiveness and diminishing unnecessary burden. To promote specific initiatives in this regard, the NIH established as a key element of its Roadmap effort a new Clinical Research Policy Analysis and Coordination (CRpac) Program.

CRpac's goal is to create a trans-government forum for stimulating the harmonization, streamlining, and optimization of policies and requirements pertaining to the

conduct and oversight of clinical research. CRpac staff thus work closely with other Federal agencies and offices that have responsibilities related to the funding and oversight of clinical research, including the Office for Human Research Protections, the Food and Drug Administration, the Department of the Veterans Administration, the Department of Defense, and other Federal agencies that have adopted the "Common Rule" for human subjects protections. Ensuring the more effective protection of research participants, as well as promoting the more efficient translation of research findings into clinically useful products, are two major aims of this program.

Some specific foci of the CRpac program include harmonizing diverse adverse event reporting requirements; clarifying policy where variability in the interpretation of the human subjects regulations exists; providing guidance on the use of IRBs and DSMBs; and stimulating a dialogue and consensus on clinical trial design issues to advance the science, safety, and ethics of translational research.

Question. Again, what do you need in the way of legislative authority to meet the demands placed on these academic health centers?

Answer. NIH has sufficient legislative authority and flexibility to meet the demands placed on academic health centers.

ALZHEIMER'S DISEASE

Question. For the past several years this Subcommittee has consistently encouraged NIH to assign a high priority to research on Alzheimer's disease. In fiscal year 2002, the Subcommittee went so far as to encourage NIH to boost its investment in Alzheimer's disease research to $1 billion. But despite the steady increase in appropriations for the Aging Institute, I understand that your investment in Alzheimer research actually declined by nearly $20 million between fiscal year 2003 and fiscal year 2004. Would you explain how that could possibly happen?

Answer. It is true that NIH funding for Alzheimer's disease (AD) research—for which the National Institute on Aging (NIA) is the lead NIH institute, although several NIH Institutes support AD research—decreased from fiscal year 2003 to fiscal year 2004. Since its inception in 1974, the NIA has placed a very high priority on Alzheimer's disease and AD-related research, such that AD has received by far more funding by NIA than any other aging-related disease research. In fiscal year 2004, despite the Institute's best efforts, which included the funding of a major new multimillion dollar initiative, the Alzheimer's Disease Neuroimaging Initiative, the NIA—and to a lesser degree, the NIH as a whole—experienced its first-ever decrease in AD funding.

In fiscal year 2004, the number of Research Project Grant (RPG) applications submitted across all NIA programs was unusually high, up 40 percent from fiscal year 2003. This made fiscal year 2004 a very competitive year overall for RPG funding at NIA. Of the applications the Institute received that were judged highly meritorious in peer review, considerable more dealt with other diseases and conditions included in the NIA mandate, while far fewer were AD-related, than in the preceding year. This was highly unusual, and there is every expectation that it will not re-occur and that funding for AD-related research will increase in fiscal year 2005.

Question. Can you give the Subcommittee some assurances that this will not occur again?

Answer. An immediate assurance can be offered to the Subcommittee that Alzheimer's disease research continues to be a high priority for the NIA, and that the situation is being continually monitored and proactive steps have been taken that should prevent the re-occurrence of this unanticipated situation. So far during fiscal year 2005, AD research applications have been more competitive in peer review than this time last year, so that AD-related awards are outpacing non-Alzheimer's disease awards. In addition, $8 million of approximately $10.2 million available for new NIA initiatives in fiscal year 2005 has been allocated for AD initiatives. Finally, the fiscal year 2005 Centers allocation will provide an increase in the AD Centers program funding of at least 1.5 percent above fiscal year 2004.

We are continuing to monitor the situation closely, but currently fiscal year 2005 AD funding is on track and consistent with application success rates seen in previous years. If this rate continues through the rest of the fiscal year, fiscal year 2005 AD funding will most assuredly be higher than fiscal year 2004.

[In millions of dollars]

	Fiscal year			
	2003	2004	2005	2006
Alzheimer's Total NIH	658	633	647	649
Aging Institute share	(502)	(483)	(496)	(498)

POLYCYSTIC KIDNEY DISEASE

Question. The National Institutes of Health in general—and the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], in particular, has—under your NIH Roadmap to the Future initiative—focused anew on translating basic research discoveries into therapeutic interventions to treat/cure some of the world's most prevalent life-threatening diseases, including polycystic kidney disease or PKD . . . the most common life-threatening genetic disease affecting 600,000 Americans. I would appreciate your comments about whether the discovery of the PKD genes in 1994/1995 culminating in the current clinical drug trial for PKD in humans—enabled by research partnerships between the Federal government (via NIDDK), private funding sources, and industry, combined with innovative technological advances such as provided from the CRISP study—is an example of what was envisioned in the development of the NIH Roadmap initiative, and—if so, in what respects?

Answer. The intent in developing the NIH Roadmap for Medical Research was to tackle very broad scientific challenges and thereby to generally move translational research forward for the benefit of all. Thus, NIH Roadmap initiatives are not specific to any particular diseases, but are expected to yield benefits for a wide range of diseases. While not directly funded under the Roadmap, the PKD research you cited—such as the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study—is indeed consistent with the vision of the broader NIH Roadmap for Medical Research. The CRISP study has been a successful collaborative effort of imaging specialists and clinicians focused on PKD. The focus of the CRISP study is investment in the groundwork that will facilitate the development and eventual testing of clinically practical intervention strategies for PKD. The CRISP investigators have used state-of-the-art imaging techniques to develop new non-invasive methods that can reliably assess PKD progression. Such methods are important as they will facilitate design of future clinical trials of new therapies for PKD, which will likely require shorter follow-up periods and fewer patients than current trials of kidney disease. Similarly, it is hoped that NIH Roadmap initiatives will, among other things, provide technologies and other resources to facilitate discovery and characterization of disease genes; integrate expertise from multiple disciplines to more effectively attack problems in health and disease; enable more rapid testing of promising therapies in animal models of disease and in humans; and promote partnerships between the public and private sectors. By optimizing scientific tools and removing barriers to progress for researchers across all research fields, the NIH Roadmap should help pave the way to an accelerated pace of discovery from the bench-to-the-bedside for specific diseases such as PKD.

Question. In testimony before Congress on April 22, 2004, Dr. Allen Spiegel, the Director of NIDDK, said that "PKD represents an intersection of public health need, scientific opportunity and input from stakeholders regarding research directions, and that the NIDDK—working in conjunction with patient groups, such as the PKD Foundation, and investigator groups, such as the American Society of Nephrology—resulted in a strategic plan to exploit research opportunities, engage in expanded molecular research, develop new animal models and establish four PKD Research Centers." In sum, he said NIDDK is committed to moving the research agenda forward toward the goal of developing more effective diagnosis, treatment and prevention of disease. Therefore, considering these developments and the fact that the prime cause of death for PKD patients is chronic cardiovascular disease, that PKD patients suffer greatly from psychosocial problems like depression, anxiety and suicide due to PKD's chronic nature, and the recessive form of PKD has such a high rate of morbidity and mortality in neonates and infants, to what extent is NIH considering "inter-institutional" research involving NIDDK, NHLBI (the National Heart, Lung and Blood Institute), NICHD (National Institute of Child Health & Human Development) and the NIMH (the National Institute for Mental Health) as a means to uncover potential interventional methods which could address these significant co-morbidities?

Answer. There are two major avenues through which the NIH is able to pursue collaborative research opportunities and initiatives on the co-morbidities of PKD

and other chronic kidney diseases. First, the statutory Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee (KUHICC)—chaired by the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK)—encourages cooperation, communication, and collaboration among all relevant Federal agencies. Meetings of the Kidney Diseases Subcommittee provide an important opportunity for the NIH Institutes and Centers to initiate collaborations on shared interests in kidney disease.

Second, as the lead Institute for research on chronic kidney diseases, including PKD, the NIDDK has spearheaded collaborative efforts to address many of the comorbidities experienced by PKD and other chronic kidney disease patients. Let me provide a few examples. A major new collaborative study being led by NIDDK, with participation of the NICHD, the NHLBI and the NINDS, is the Pediatric Chronic Renal Insufficiency Cohort Study ("CKIDS"). This important new undertaking will address the impact of chronic kidney disease on cardiovascular morbidity as well as neurocognitive development and emotional health; it will include children with both the recessive and dominant forms of PKD. In a related area, an initiative on chronic illness self-management in children is currently being supported by the NIDDK, NHLBI, NICHD, and the National Institute on Nursing Research. The NHLBI convened a working group, "Cardio-Renal Connections in Heart Failure and Cardiovascular Disease," on August 20, 2004 to further understanding of the interaction of the heart and the kidney in cardiovascular disease. The NHLBI is also a cosponsor of a planned NIDDK program announcement "Pilot and Feasibility Program Related to the Kidney" to foster the development of high-risk pilot and feasibility research; it is anticipated that this PA will be issued in 2005. In 2001, the NIDDK collaborated with the NIMH and the NIH Office of Behavioral and Social Sciences Research (OBSSR) in holding a major conference to determine the state of knowledge with regard to the co-morbid condition of depression in patients with diabetes, kidney disease, and obesity/eating disorders, and to propose a research agenda for the future. Finally, NHLBI and NIDDK have created a working group to address the relationship between hypertension and kidney disease, and are working collaboratively to design new initiatives in this area. All of these collaborative activities complement NIDDK's continuing efforts to address comorbidities of chronic kidney disease, such as the Chronic Renal Insufficiency Cohort (CRIC) study, which is examining the relationship between cardiovascular disease and chronic kidney disease in adults, in order to try to find opportunities to prevent and better treat both. Another example is the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial, which is testing whether treatment to lower total homocysteine levels using a high-dose combination of folic acid, vitamin B12, and vitamin B6 will reduce cardiovascular damage in kidney transplant recipients. Both of these large studies include substantial numbers of patients with PKD.

BASIC BEHAVIORAL RESEARCH

Question. As a matter of some concern I would like to bring to your attention an item relating to the National Institute of General Medical Sciences. I would also like to include Dr. Berg, as Director of NIGMS, on this item.

Dr. Zerhouni, for the past seven years, starting in fiscal year 1999, the Committee has included report language urging NIGMS to fund basic behavioral research and training. two years ago, Senator Inouye, Senator Harkin, and I had a colloquy on the senate floor expressing the Committee's strong support for basic behavioral research and training. Following the colloquy, I know the NIH commissioned a Task Force to study the matter and report back to the Director's Advisory Committee. I understand that report was made available to you and your Advisory Committee last December and it, too, very strongly urged that NIH initiate such a program and create an Institutional presence for it in an Institute like NIGMS.

Dr. Zerhouni, what are your plans to implement a basic behavioral research and training program at NIGMS?

Answer. In keeping with the preferred approach of performing portfolio analysis across NIH rather than on an institute-by-institute basis, a working group of the Advisory Committee to the Director, NIH, was formed to examine basic behavioral research across NIH. The working group reported to the Advisory Committee on December 2, 2004. Their analysis revealed that the institutes and centers (including NIGMS) supported approximately $2.68 billion in behavioral research, including approximately $936 million in basic behavioral research, in fiscal year 2003. In addition to this base, several components of the NIH Roadmap for Medical Research are directed toward basic behavioral research. In particular, several mechanisms are being used to stimulate interdisciplinary research at the interface of the behavioral/social and biological sciences, provide the interdisciplinary training necessary for

postdoctoral investigators to work in these areas, and support development of innovative methods and technology that will facilitate research at the intersection of the behavioral, social and biomedical sciences.

Following the submission of the working group report, NIGMS has taken several steps to more clearly articulate the basic behavioral research it supports, encourage the submission of more research applications in these areas, and increase the number of investigators who can work at the interface of the behavioral and biological sciences:

Research Training at the Interface of the Behavioral and Biological Sciences.—Basic behavioral research is of critical importance to the mission of the NIH and can play a crucial role in understanding the etiology of disease and enhancing preventive and therapeutic inventions. Greater understanding of the molecular, genetic, and neural processes governing behavior, and the reciprocal effects of behaviors on physiological processes, is crucial for a complete understanding of human health and those diseases in which behavior is a risk factor, diagnostic indicator, or symptom. To advance our knowledge in these areas, researchers will need to integrate multiple disciplinary perspectives, methodologies, and levels of analysis. NIGMS has a strong background in developing and supporting such interdisciplinary research training. While some existing NIGMS training programs such as the Medical Scientist Training Program and the Systems and Integrative Biology program include elements of the behavioral sciences, there has not been a program dedicated to training at the basic behavioral science-biological science interface. NIGMS has developed a proposal for such a predoctoral program and is coordinating its further development with other NIH Institutes having an interest in this area.

Collaborative Research on Basic Mechanisms of Behavior.—To encourage the multidisciplinary research that is needed for a fuller understanding of the basic mechanisms of behavior, NIGMS has proposed an initiative to facilitate collaborations between basic behavioral scientists and investigators with expertise in state-of-the-art genetics, molecular biology, and genomics. It is anticipated that this collaborative research, performed with model organisms, will either enhance existing models or lead to the development of new models of normal or abnormal human behavior. The concept for this solicitation is to be presented for approval at the May 2005 meeting of the National Advisory General Medical Sciences Council.

Assessing Interactions Among Social, Behavioral, and Genetic Factors in Health.—NIGMS is a major contributor to an Institute of Medicine committee examining the state of the science on gene-environment interactions that affect human health. The study will identify approaches and strategies to strengthen the integration of social, behavioral, and genetic research in this field as well as consider relevant training and infrastructure needs. The results of this study will be used by the NIH to guide its programs in these areas.

WORK WITH PUBLISHERS

Question. I know that you are putting together an Advisory Working Group to provide advice on implementation of the NIH Public Access policy. I understand that the Working Group will not be able to convene prior to the May 2nd implementation date of the new policy.

Publishers are eager to work with you as they formulate their own policies for accommodating the NIH policy. They are important to the success of the NIH plan and I urge you to consult with them before May 2nd, as you finalize the details of the implementation policy.

Do you plan to consult with stakeholders before finalizing the details for implementing the access policy?

Answer. Throughout the implementation phase, we have had inquiries from and communicated with a number of publishers and members of the library community concerning the operation of the submission system. The initial submission system has been designed to enable individual investigators to submit their manuscripts in keeping with the basic goals of the Policy. We plan to seek feedback from users, and we will make system enhancements based on substantial input from all stakeholders, including publishers, to facilitate submissions in the future by others designated to do so for the authors.

Question. Given that your policy is to take effect May 2, can you outline the process NIH is following to assure such representation, and whether you expect to have scientific publishers identified and cleared for membership by May 2?

Answer. Invitations to Working Group members have been made. The following publishers have accepted and will be participating in the Working Group: Jeffrey M. Drazen, M.D., Editor-in-Chief, New England Journal of Medicine; Brian Nairn, Chief Executive Officer, Health Sciences; Elsevier Mark E. Sobel, M.D., Ph.D., Exec-

utive Officer, American Society for Investigative Pathology; and Annette Thomas, Ph.D., Managing Director, Nature Publishing Group

SPINAL MUSCULAR ATROPHY

Question. It is my understanding that the new Spinal Muscular Atrophy "model" for preclinical research and development for candidate therapeutics is in place. Please outline the applicability of this model to Muscular Dystrophy.

Answer. The SMA Project, which is now underway, represents a new and as yet untested approach for developing therapies for diseases that meet certain criteria essential to a highly targeted therapy development strategy. SMA is a consequence of inherited mutations in the SMN1 gene. The SMN2 gene product has a very similar function to that of SMN1; thus, increasing the expression of the intact SMN2 gene was both a rational and plausible mechanism for therapeutic development. Moreover, since research had already identified several chemical structures with the biologic activity of increasing SMN2 protein expression, there was a consensus that development of drugs targeting SMN2 expression represented the best pathway for SMA treatment development. In sum, the key traits in the design of the SMA project were: (a) a consensus pathway to SMA treatment development, such that resources were not diverted away from other, potentially successful, strategies and (b) the availability of lead chemical compounds on which to base drug development. It remains to be seen whether the unique drug development strategy that was selected for the SMA pilot program will be sufficiently effective to warrant its consideration for other neurological disorders.

The important question with respect to MD is not whether the SMA model could be applied to MD in some way, but whether it is the best possible approach to apply the resources available for MD therapy development. There were critical criteria used in the NINDS's design of the SMA project (consensus on strategy and availability of lead compounds) that do not currently apply to MD. In the area of MD, there are at least five or six potential strategies under active study, any of which may prove to be effective in the treatment of MD. These strategies range from those that have a relative high probability of success in delaying the loss of muscle mass and thereby augmenting quality of life, to those that have a higher risk of sort-term failure but in the long run may more dramatically increase both quality and length of life. At this point in time, there is no consensus on any one strategy for emphasis, since the potentially most successful strategy is not nearly as clear as it was for SMA. Instead of choosing to divert resources to any one of a number of plausible strategies in MD therapy development, the NIH is making parallel investments in all of the strategies. As research progresses along these multiple, parallel pathways, their relative potential for therapeutic development and availability of candidate lead compounds likely will change and the NIH would adjust its aggressive pursuit of an MD therapy accordingly. Unless an arbitrary choice was made to exclude potentially successful treatment strategies in order to provide the necessary focus, an SMA-type program is not applicable to MD.

Question. The committee understands that the SMA Model statement of work is based upon an NIH Strategic plan developed by a steering committee. How does this separate steering committee reconcile research priorities with the NIH Director's strategic vision?

Answer. The formal statement of work for the Spinal Muscular Atrophy (SMA) Project was developed by the NINDS scientific and contract staff to specify what services the contractor for the SMA Project would provide. The NINDS recruited the scientists and physicians on the SMA Project steering committee from industry, academia, the FDA, and the NIH based on their expertise in drug development and areas relevant to SMA. NINDS scientists serve on this committee in an ex officio capacity. This committee is advisory to NINDS, and the recommendations of the committee are implemented by NINDS in the context of the Director's strategic vision for NIH, which emphasizes applying innovative approaches to translate basic science progress into the development of therapies.

Question. Please outline NIH assessment of the technical and contractual risk associated with the SMA model.

Answer. There are two major aspects of risk associated with the SMA Project, neither of which can be meaningfully quantified. First and foremost, the scientific challenges of developing a therapy for a neurogenetic disorder are enormous. Medical science, despite extensive efforts, has had few successes so far in this endeavor for many reasons, not the least of which is the complexity of the nervous system and its diseases. Thus, the goal of developing a therapy within four years to the point that it is ready for human testing is extremely ambitious. This is one of the reasons that the selection criteria for the first disease of focus were necessarily stringent,

and explains why the project must focus on one basic therapeutic strategy in order to move quickly toward the goal. The second aspect of risk concerns the structure of the program itself. The program is intended to expedite therapy development, but several aspects of the project are novel and untested, so whether it will indeed be an efficient and effective use of resources remains to be seen. In effect, the SMA Project must develop de novo a virtual drug company and develop a drug. It has proven challenging to identify contractors who are willing and able to perform services in disease areas that are outside the normal scope of their operations, particularly with such a rapid and restricted time line. Once the contracts are in place, the coordination of the various efforts and the marshalling of the whole toward accomplishment of the goal present considerable organizational, as well as scientific challenges, as evidenced by the high failure rate among even established biotechnology and pharmaceutical companies in this type of endeavor. It is difficult to anticipate what hurdles might arise in such a novel undertaking.

Question. The committee understands that the SMA model was chosen because of the state of scientific understanding of this disease. What are the specific metrics and measures of merit for this determination?

Answer. The NINDS chose SMA as the focus of the SMA Project because this disease best met the criteria that are critical for success of a narrowly focused approach to therapy development. These criteria include: (1) severity of disease (2) scientific readiness—which includes a defined genetic cause (loss of the SMN1 gene), a consensus strategy for treatment (increasing the SMN2 gene product), and the availability of "lead" chemical compounds. The focus of the SMA Project is a type of translational research that is normally conducted only in industry settings, which is the chemical conversion of an active chemical compound into a drug that is safe enough for human testing. Applying this strategy relies on the availability of "lead" chemical compounds that have a desirable biological activity and have the potential to be chemically improved for human use. Most importantly, previous academic and privately funded efforts had applied this strategy and identified small drug-like molecules with the desired activity, and the SMA Project is optimizing the activity and pharmacology of these molecules to make them suitable for clinical testing.

Question. What would be the comparable level of understanding in MD research that would justify an MD model for translational research?

Answer. Like SMA, MD is a severe, debilitating disease, and for some of the forms of MD, there are defined causes. However, unlike SMA, there is no consensus strategy for treatment, there is no single biological activity to target for treatment, and there are no "lead" compounds identified as potential therapeutics.

In the case of Duchenne MD, there are several quite different and equally promising approaches to develop therapies. These include strategies to replace the defective gene, to repair that gene, to alter gene splicing, to override premature gene stop codons, to upregulate potentially compensatory genes, to increase the regenerative capacity of muscle by providing various trophic substances or by blocking the effects of growth inhibiting substances, to reduce the rate of muscle degradation by blocking various components of that process, and to replace cells via stem cells or progenitor cells. Unfortunately, none of these approaches have yet yielded the drug-like molecules that could form the basis of a drug development program for MD to the same degree that these are available for SMA, and the goal of identifying promising leads in these approaches to therapy development for MD is better served by a more diverse and competitive approach. The narrow focus of optimization efforts applied in the SMA Project will only be relevant to MD once these leads have been identified.

The NIH is aggressively investing resources in translational research for MD through other mechanisms. These include the Wellstone Muscular Dystrophy Centers, the NINDS Cooperative Program in Translational Research, and investigator initiated research grants. Given finite resources, undertaking an SMA Project for MD at this time would require the NIH to divert funds from these other programs. The broad-based approach that the NIH is currently pursuing is the more appropriate way to advance MD translational research at this time.

MUSCULAR DYSTROPHY CENTERS

Question. Please outline for the committee how MD centers are promoting translational research from advancements in basic MD research.

Answer. Several of the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers are supporting projects on translational research, which is research designed to take basic research to the stage of clinical testing. For example, investigators at the University of Washington are doing translational research in dystrophic mice that is designed to lead to a phase I clinical trial of gene therapy

for Duchenne MD (DMD). Researchers at the University of Pittsburgh are also exploring methods for improved gene delivery using an adeno-associated virus (AAV) in a canine model of MD. AAV is a viral vector (the "delivery vehicle" for a gene) that has been designed to carry a mini-dystrophin gene to a specific muscle location. If successful, this technique could allow the muscle to become more resistant to injury and restore function. A second translational study at the University of Pittsburgh center is using a dystrophic mouse model to explore the delivery of normal muscle derived stem cells to diseased heart tissue. The newest center at the University of Iowa will study the use of stem cell and novel gene therapy strategies for MD. One project in particular will study the development of mouse embryonic stem cells as therapeutic tools for muscular dystrophy. This center will also emphasize study of muscle membrane repair mechanisms that could lead to an alternative strategy for treatment of MD.

An essential component of the Wellstone Centers program are the research cores at each center, which are developing improved research resources for use by the entire MD research community to accelerate translational research. For example, the core modules at the University of Washington are developing research and clinical grade gene transfer vectors and these vectors will be studied for their utility in gene therapy for the muscular dystrophies. The Wellstone Center at the University of Rochester uses one of its core modules to serve as a repository of resources, including cell lines, animal models, small molecules, and autopsy tissue. Core modules at the University of Pittsburgh support translational and clinical studies in clinical vector production for gene therapy. One of the cores within the new University of Iowa center will develop new in vitro models by inactivating genes that cause the various types of MD in an existing human embryonic stem cell line.

Collaboration and coordination among the Wellstone Centers is another important component of the Centers program, and the Centers are awarded funds to support these collaborative efforts. Currently, the Wellstone Centers are using these funds to support two dog colonies—one at University of Missouri and one at the Fred Hutchinson Cancer Research Center—as a national resource for research in MD, and working to ensure that these colonies are maintained and available for translational research. The dog MD models appear to have a phenotype that is very similar to that of Duchenne MD patients. The dog model is also important for assessing immune problems that may be associated with vectors used for gene therapy; thus, testing in the dog is an important stage after initial work in mouse muscular dystrophy models. These dogs are currently being used by researchers at a number of the Wellstone centers, as well as other researchers in the MD field.

MUSCULAR DYSTROPHY

Question. Muscular Dystrophy researchers are exploring various avenues for therapeutic solutions, which include small molecule compounds, gene therapy and stem cell research. Please outline for the committee efforts in integrating these research efforts and prioritizing research investment strategies.

Answer. NIH-funded researchers are pursuing a number of strategies to develop treatments for the MDs. These encompass drug-based (such as small molecule compounds), gene-based (such as gene therapy) and cell-based (such as stem cells) approaches. For example, several studies are aimed at developing drug-based therapies to protect muscle mass and slow muscle degeneration by blocking various components of the degenerative process. Compounds such as protease inhibitors and glycosylating enzymes are potentially promising in this area. Other studies are pursuing strategies to enhance muscle repair and regeneration mechanisms to slow, and possibly stabilize muscle degeneration by either providing various trophic substances or by blocking the effects of growth inhibiting substances. In addition, NIH-funded researchers are optimizing cell-based muscle replacement strategies, particularly strategies using stem cells or progenitor cells to populate skeletal and cardiac muscles with muscle fibers that express the absent proteins. Scientists are also developing and testing strategies for gene replacement therapy, including both gene or drug therapy strategies to replace the defective gene or increase expression of functionally homologous or compensatory genes. Finally, genetic modification therapies are being studied to bypass inherited mutations, using, for example, drug and antisense oligonucleotide exon skipping strategies.

NIH is taking steps to ensure integration and coordination of these research efforts. For example, coordination of research efforts at the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers is facilitated by a Steering Committee made up of representatives from the Centers and from the NIH institutes that fund them (NIAMS, NINDS, and NICHD). The steering committee's goal is to maximize collaborative utilization of the unique resources in infrastructure, exper-

tise, and clinical recruitment created by the Wellstone Centers. This integration is particularly important in the areas of gene therapy and stem-cell based treatment strategies as a number of the Centers have projects and support cores focused on these two areas.

Integration of research efforts and prioritization of strategies is also an important function of the Muscular Dystrophy Coordinating Committee (MDCC). This summer, a scientific working group will meet to develop and prioritize specific research aims based on broad research goals in the Muscular Dystrophy Research and Education Plan developed by the MDCC. Treatment strategies is one of the programmatic areas addressed in Plan and includes approaches such as developing effective gene therapy techniques, optimizing potential cell-based therapies, and pursuing pharmacological treatment approaches. The working group will not only prioritize research strategies, but will also identify additional obstacles and barriers to the progress of MD research and treatment, noting those that are likely to be addressed through ongoing research and programs, and those that might benefit from additional emphasis. At the next meeting of the MDCC (November 2005), the MD Scientific Working Group recommendations will be presented for discussion by MDCC member agencies.

The MDCC also serves as a venue to coordinate research efforts among member agencies and organizations. The November 2005 MDCC meeting will have a specific focus on translational research, examining the relationship of current translational efforts by the NIH, the Department of Defense, the Muscular Dystrophy Association, and Parent Project Muscular Dystrophy. This meeting will identify the translational research strategies that are currently supported by federal agencies and advocacy groups and will reinforce efforts to minimize overlap and maximize utilization of resources available for MD.

Question. Please outline for the committee the specific translational research efforts for MD; indicating their relative maturity. What percentage of research is investigator-initiated versus Institute generated?

Answer. Translating scientific advances into therapies that can help people with muscular dystrophies is a very high priority for the NIH, and multiple strategies for therapeutic development are currently being pursued. The relative maturity for the most promising of these translational research approaches and some of the NIH-funded research and research initiatives in these areas are described below. These approaches are presented in ascending order of risk and projected development time, starting with the lowest risk and shortest time frame. The risk/development time assessments should be recognized as estimates, and those that are most easily achieved may dramatically improve quality of life for muscular dystrophy patients but are not the cures that may be possible from higher risk/longer time frame approaches.

Blocking the loss of muscle mass.—Muscle fiber degeneration and the profound loss of muscle mass is the most visible consequence of MD and is directly responsible for progressive deterioration of muscle function in several types of MD. Strategies to block muscle fiber degeneration have shown promise. For example, several studies have shown that systemic treatment with a protease inhibitor reduces muscle membrane damage and ameliorates muscle degeneration in the mdx mouse model of DMD. Investigators in the NINDS intramural research program are currently pursuing the use of a protease inhibitor as a therapeutic strategy in MD patients.

A project has also been approved for funding through the NINDS's "Cooperative Program in Translational Research" for development of protease inhibitors that may be capable of delaying muscle degeneration in a variety of types of MD.

Enhancing muscle regeneration mechanisms.—Muscle has an inherent repair capacity that allows it to overcome damage but this mechanism appears to be overwhelmed in MD. NIH-funded researchers have identified genes that regulate muscle regeneration; these represent potentially important therapeutic targets for MD. One of these genes, GDF8 or myostatin, inhibits muscle development and regeneration. Myostatin inhibition studies using molecular genetics or a specific blocking antibody suggest that the strategy can increase muscle mass in several types of MD. The very recent development of a strategy using an endogenous myostatin inhibitor may hold promise. Alternatively, growth factors that promote muscle growth and regeneration also have shown promise as a therapeutic strategy.

Replacing degenerating muscle with new muscle derived from stem cells.—Muscle and other tissues contain stem cells that can be directed to form muscle fibers. There has been considerable progress in isolating and expanding stem cells, directing their fate, targeting them to dystrophic muscle, and using imaging technology to monitor the efficacy of stem cell transplantation. Overcoming the host immune

response is one of the significant obstacles to the success of cell-based therapy in MD.

A project at the Wellstone Center at the University of Pittsburgh is focused on delivery of stem cells to diseased muscle, while the Center at the University of Iowa will use one of its cores as a stem cell resource for the MD community. In addition, a project funded as a result of an NIH program announcement entitled, "Muscular Dystrophy: Pathogenesis and Therapies," as well as other NIH-supported studies, are exploring how to coax stem cells to become skeletal muscle cells with the ultimate goal of transplanting these differentiated cells.

Gene therapy.—Gene targeting to replace a defective gene must overcome the problems of accessing the muscle tissues and avoiding an immune response to the delivery system. In addition, the large size of the dystrophin gene—in the case of Duchenne MD—has necessitated the development of novel vectors and mini-dystrophin and micro-dystrophin constructs. NIH-supported research has made considerable progress in these areas. Dystrophin constructs that are capable both of restoring muscle function and of being contained in the AAV vectors have been generated and tested in animal models. An additional obstacle in gene therapy is delivering the gene construct to sufficient numbers of muscle fibers such that muscle function is improved. Delivery systems are currently being tested for achieving the goal of treating MD patients.

A number of projects at the Wellstone Centers are pursuing gene therapy strategies, and the research cores at two of the Centers are developing tools for use in gene therapy studies, as outlined earlier. The NINDS Cooperative Program in Translational Research also recently funded a major project that brings together a team of basic and clinical scientists to carry out the steps necessary to bring gene therapy for Duchenne MD to readiness for clinical trials. In addition, the program announcement, "Muscular Dystrophy: Pathogenesis and Therapies," has resulted in a number of funded projects focused on developing novel or modified vectors, using mini-dystrophin constructs, and studying ways to effectively deliver the genes to muscle.

Genetic strategies to bypass the mutations that cause MD.—Other approaches to correct a defective gene besides gene replacement are also being pursued. For example, antisense oligonucleotide (AO) technology may be used to skip, or splice out, those portions of the gene containing mutations and then produce a shortened, but still functional protein. Through research in cell culture and in animal models, AO administration has been shown to enhance expression of normal dystrophin protein. Studies supported by the NIH have made critical breakthroughs in AO technology and in demonstrating proof of principal in cell culture. While this technology is very promising, the delivery of AOs is subject to the many of the same obstacles as in the gene therapy studies described above. Other approaches include the use of drugs to produce "read-through" past the gene defect. An NINDS-supported clinical trial for gentamicin-mediated read-through in DMD patients is underway.

Both of these approaches—AO therapy and identification of compounds to promote read through—are being pursued in studies funded as a result of the program announcement, "Muscular Dystrophy: Pathogenesis and Therapies."

It is difficult to estimate the percentage of MD translational research that is investigator-initiated versus institute generated, although the NIH MD portfolio contains a significant amount of both types. Investigators may submit a grant to the NIH as part of the regular submission process, or in response to a particular Institute-generated initiative. The NIH Institutes, with considerable input from the research community, have been working to develop initiatives and programs to stimulate translational research in the MDs. For example, in April 2005, NIAMS announced a request for applications for Centers of Research Translation. Furthermore, NIH is currently developing a translational research initiative specific to MD, which will stress the milestone-driven approach to research and will include substantial project development and grant management interactions with NIH program staff.

Question. Accelerated review of research proposals remains a concern for patient advocacy groups and the committee. Please outline for the committee all efforts NIH has undertaken with the Center for Scientific Review to expedite review decisions. Please provide supporting data regarding the length of time from RFP to award on MD related research.

Answer. NIH's peer review process is widely recognized as the cornerstone of the remarkable success of the NIH extramural program. The NIH Center for Scientific Review (CSR) receives all grant applications submitted to NIH (approximately 75,000 per year), logs them in, refers these applications to a peer review panel to be evaluated on technical and scientific merit, and identifies a potential funding source at NIH. The majority of applications that come to NIH are reviewed by CSR,

while the remaining ones are reviewed by specific institutes, in particular those that are received in response to a specific solicitation.

Currently, the interval between NIH receiving an application and the application being considered for funding is typically 6–7 months. For example, in the case of the Senator Paul D. Wellstone MD Cooperative Research Centers, applications in response to the first Request for Applications (RFA) were received in February 2003, and awards were made in September 2003. NIH and CSR are considering ways to reduce this interval. However, it is essential that efforts to speed the process do not compromise the core values of NIH peer review system—a thorough and fair review of the application by a review panel with the appropriate scientific and technical expertise. One approach to accelerate the review cycle is the electronic receipt of applications. NIH is now accepting several types of grant applications electronically and will continue to introduce electronic receipt of other application types. When electronic receipt of grant applications is fully implemented at NIH, the system should offer considerable time savings because data, which in the past have been manually entered, will be automatically captured as soon as applications are submitted. In addition, it may be possible to automatically analyze some of the data initially captured during electronic receipt and streamline the referral process, thereby offering additional time savings.

Expediting review of grant applications while maintaining review quality is a high priority for NIH. To underscore this, Dr. Zerhouni has recently created a new NIH Peer Review Advisory Committee to provide guidance on developing ways to advance NIH peer review and ensure its vitality. In addition, in March 2005, Dr. Zerhouni named a new CSR Director, Dr. Antonio Scarpa. When Dr. Scarpa begins work on July 1, 2005, he is expected to place a high priority on the goal of compressing the peer review cycle.

PEER REVIEW ON MUSCULAR DYSTROPHY

Question. Continuity in Peer Review for Muscular Dystrophy research remains a concern. Please outline for the committee all efforts to ensure peer reviewers' areas of expertise encompass the full body of muscular research.

Answer. The peer review of the majority of applications received by NIH is conducted at the Center for Scientific Review (CSR). In response to concerns expressed by the MD community, a working group of the Center for Scientific Review (CSR) Advisory Committee met in March 2001 to evaluate the review of skeletal muscle biology research applications. The Skeletal Muscle Biology Working Group was composed of 17 leading scientists in the field and several NIH staff. A particular concern of the working group was the locus of review for muscular dystrophy applications. Ultimately, the working group recommended the formation of a Skeletal Muscle Biology Special Emphasis Panel (SMB SEP). Nearly all muscular dystrophy related research applications reviewed by CSR were to be reviewed in this committee. The SMB SEP met for the first time in October 2001.

The Skeletal Muscle Biology Working Group offered this recommendation as an interim solution pending recommendations to be made by the larger Musculoskeletal, Oral and Skin Sciences (MOSS) Study Section Boundaries Team (also a working group of the CSR Advisory Committee) that was scheduled to meet in July 2001 as part of a CSR-wide reorganization process. The MOSS Team meeting in July 2001 drew heavily on and expanded the recommendations of the Skeletal Muscle Biology Working Group. The MOSS Team recommended elevating the status of the review group from a special emphasis panel to a permanent regular study section. This recommendation was accepted by the CSR Advisory Committee, and a new regular study section named Skeletal Muscle Biology and Exercise Physiology (SMEP) was implemented. The last meeting of the SMB SEP was in June 2003 and the first meeting of the SMEP study section, its successor, was in October 2003. The SMEP study section is now the primary locus of review for muscular dystrophy related research applications at CSR.

The range of science in the applications reviewed by SMEP is extremely broad, spanning fundamental molecular biology to therapeutic interventions. To match this breadth, the committee is composed of a number of individuals with the expertise necessary to cover these varied topics. Eleven of the regular members assigned to review these applications are noted investigators who themselves conduct muscular dystrophy related research. As members rotate off the committee they are replaced by individuals with a similar background—five new members have been nominated for the coming year. In addition, to supplement this broad expertise, the committee has used twelve temporary members who also are involved in conducting muscular dystrophy related research.

As stated above, the majority of applications received by NIH are reviewed by CSR. In contrast, applications that respond to specific initiatives are reviewed by individual NIH Institutes. Like CSR, the Institutes are also committed to ensuring that individuals with the appropriate expertise review applications, and continuously work to identify and invite scientists with specific knowledge and appropriate background to participate in the review of applications.

QUESTIONS SUBMITTED BY SENATOR JUDD GREGG

UMBILICAL CORD BLOOD STEM CELLS

Question. Given that Umbilical Cord Blood Stem Cells are already being used to treat over 70 life threatening diseases, should the National Institutes of Health take steps to educate the public, and if so, how should education take place?

Answer. The NIH scientists address questions from representatives of the news media and the public who directly contact the NIH. In addition, NIH scientists speak at conferences that are convened by professional and public interest organizations and they provide advice to the Health Resources and Services Administration in the development of a national cord blood bank program. Future directions for public education would involve convening a strategy development workshop of researchers and relevant stakeholder groups to determine what is currently being done to address education issues, identify major education gaps, and recommend and prioritize specific education outreach activities and areas requiring further research.

In addition to these efforts, the NIH maintains a stem cell information website at http://stemcells.nih.gov. The NIH Stem Cell website is frequently visited by individuals seeking information on stem cell research, including cord blood stem cells. For example, the website has an NIH report entitled "Stem Cells: Scientific Progress and Future Research Directions." This report has a chapter (http://stemcells.nih.gov/info/scireport/chapter5.asp) on hematopoietic (blood-forming) stem cells, including stem cells from the umbilical cord. Several stem cell literature databases that include cord blood stem cell research studies can also be found on the NIH website at http://stemcells.nih.gov/research/literature.asp. There are also links to several organizations, including the National Marrow Donor Program® and the International Cord Blood Society, that have informational sites on cord blood stem cells. The website also contains a "Frequently Asked Questions" section (http://stemcells.nih.gov/info/faqs.asp#umbilical) with information on "Where can I donate umbilical cord stem cells?" Overall, the NIH Stem Cell website provides useful scientific information to the public about stem cell science.

Question. What research is currently being done regarding the use of Umbilical Cord Blood Stem Cells to treat disease?

Answer. The NIH currently funds clinical research to evaluate the safety and effectiveness of matched sibling cord blood transplantation in children with sickle cell anemia and thalassemia (Cooley's anemia). The first multi-center, unrelated-donor cord blood banking and transplantation study (COBLT), which was funded by the NIH, was recently completed. The COBLT study evaluated the safety and effectiveness of cord blood transplantation in adult and pediatric patients with hematologic malignancies as well as pediatric patients with inborn errors of metabolism and immune deficiencies. Its results were shared with the Institute of Medicine for a recent report on Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program. Publication of the COBLT study results is in progress.

A major obstacle to cord blood transplantation in adult recipients is the limited hematopoietic stem cell dose available in a single cord blood unit. The NIH currently funds research exploring alternative approaches to optimize transplant outcome. These approaches include the transplantation of two partially matched cord blood units from different cord blood donors, use of a less toxic (non-myeloablative) conditioning regimen prior to cord blood transplantation, and expansion of cord blood stem cells in culture and their use in conjunction with non-expanded cord blood for transplantation in patients with hematologic malignant diseases. These studies are in the early phase of clinical investigation. In addition, the NIH funds the Center for International Blood and Marrow Transplant Research, which conducts registry studies to evaluate the clinical outcomes of cord blood transplantation.

The NIH also funds a variety of basic and pre-clinical research projects to examine the properties of cord blood stem cells, including the immune responses of cord blood cells during and after transplantation, the growth properties of cord blood stem cells, and conditions to improve the outcome of cord blood transplantation.

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

POLYCYSTIC KIDNEY DISEASE (PKD)

Question. In testimony before Congress last year, Dr. Allen Spiegel said the NIDDK is committed to moving the PKD research agenda forward toward the goal of developing more effective diagnosis, treatment and prevention of the disease. Considering that the prime cause of death for PKD patients is chronic cardiovascular disease, PKD patients suffer greatly from psychosocial problems like depression, anxiety and suicide due to PKD's chronic nature, and the recessive form of PKD has such a high rate of morbidity and mortality in neonates and infants, to what extent is NIH considering "inter-institutional" research involving the NIDDK, NHLBI, NICHD, and the NIMH as a means to uncover potential interventional methods which could address these significant co-morbidities?

Answer. The NIH has two major avenues for pursuing collaborative research opportunities and initiatives on the co-morbidities of PKD and other chronic kidney diseases. The first avenue is the statutory Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee (KUHICC). This Committee, which is chaired by the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK), encourages cooperation, communication, and collaboration among all relevant Federal agencies. Meetings of the Kidney Diseases Subcommittee provide an important opportunity for the NIH Institutes and Centers to initiate collaborations on shared interests in kidney disease.

The second avenue is through the activities of the NIDDK, the lead NIH Institute for research on chronic kidney diseases, including PKD. In this capacity, the NIDDK has spearheaded collaborative efforts to address many of the comorbidities experienced by PKD and other chronic kidney disease patients. Let me provide a few examples. In 2001, the NIDDK collaborated with the National Institute of Mental Health (NIMH) and the NIH Office of Behavioral and Social Sciences Research (OBSSR) in holding a major conference to determine the state of knowledge with regard to the co-morbid condition of depression in patients with diabetes, kidney disease, and obesity/eating disorders, and to propose a research agenda for the future. A major new collaborative study being led by NIDDK, with participation of the National Institute for Child Health and Human Development (NICHD), the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Neurological Disorders and Stroke (NINDS), is the Pediatric Chronic Renal Insufficiency Cohort Study ("CKIDS"). This important new undertaking will address the impact of chronic kidney disease on cardiovascular morbidity as well as neurocognitive development and emotional health; it will include children with both the recessive and dominant forms of PKD. The NHLBI convened a working group, "Cardio-Renal Connections in Heart Failure and Cardiovascular Disease," on August 20, 2004 to further understanding of the interaction of the heart and the kidney in cardiovascular disease. The NHLBI is also a cosponsor of a planned NIDDK program announcement (PA), "Pilot and Feasibility Program Related to the Kidney," to foster the development of high-risk pilot and feasibility research; it is anticipated that this PA will be issued in 2005. An initiative on chronic illness self-management in children is currently supported by NIDDK, NHLBI, NICHD, and the National Institute on Nursing Research. Finally, through a working group they created to address the relationship between hypertension and kidney disease, the NIDDK and NHLBI are working collaboratively to design new initiatives in this area. All of these collaborative activities complement the NIDDK's continuing efforts to address comorbidities of chronic kidney disease. Examples of these efforts include the Chronic Renal Insufficiency Cohort (CRIC) study, which is examining the relationship between cardiovascular disease and chronic kidney disease in adults, in order to try to find opportunities to prevent and better treat both, and the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial, which is testing whether treatment to lower total homocysteine levels using a high-dose combination of folic acid, vitamin B12, and vitamin B6 will reduce cardiovascular damage in kidney transplant recipients. Both of these large studies include substantial numbers of patients with PKD.

PUBLIC ACCESS

Dr. Zerhouni, I commend you for instituting a new policy that will increase public access to NIH-funded research. I'm hopeful that this policy will help speed the pace of scientific progress and give patients and taxpayers better access to research that they are, after all, paying for.

Question. There's still some question, though, about how many researchers will voluntarily submit their papers to PubMed Central, and how much of an embargo

time they'll require between the publication of a paper in a scientific journal and when the paper will be posted for public access. Have you considered, as a way of leading by example, requiring your own intramural researchers to deposit their final papers in PubMed Central and make those papers accessible immediately at the time of publication?

Answer. We have provided NIH staff training about the Policy and intramural research managers are now actively encouraging authors to submit manuscripts and designate public release as soon as possible. The Policy-related submissions will directly benefit NIH-supported investigators because recent studies have shown that freely available articles get cited more in other research publications. An increase in the number of citations helps improve the professional standing of investigators. Due to these benefits we anticipate that intramural authors will choose the earliest release dates.

I also believe that the voluntary nature of the final policy permits sufficient flexibility to accommodate the needs of different stakeholders and leaves the ultimate decision in the hands of scientific investigators who are in the best position to judge the circumstances and the time frame under which their work may be made accessible to the public at large. This flexibility allows authors to delay posting of manuscripts if there are concerns about the policy's adverse impact on their area of research. Therefore, we believe that by having a Policy that provides maximum flexibility, authors will respond with maximum participation.

Question. I'm also concerned that the policy could place researchers in a difficult position. It's up to researchers to negotiate with publishers to get permission to post the articles in the NIH database. Since participation is voluntary, publishers might pressure researchers not to release their work at all, or to wait a full 12 months. Do you share this concern? How will you know if this pressure is taking place?

Answer. We will be gathering statistics on grantee participation rates and their specified embargo periods. An NIH Public Access Working Group of the NLM Board of Regents has been established and includes representatives of various stakeholder groups that will advise the NLM Board of Regents on implementation and assess progress in meeting the goals of the NIH Public Access Policy. The above statistics will be presented to this Working Group and, if it appears necessary, the Working Group may suggest modifications of the policy to ensure that the public archive is sufficiently timely and comprehensive.

Question. Finally, could you provide this subcommittee with a report, as soon as possible after December 1, 2005, on how many eligible articles were deposited in PubMed Central during the first six months of the policy and what the average embargo period was. Additionally, we would like to know how many articles are in the pipeline awaiting posting. Lastly, do you have any way of tracking through PubMed the number of articles supported with NIH funds but not submitted to PubMed Central? In other words, will you be able to provide both the numerator and the denominator of the equation that will demonstrate success of your policy?

Answer. We estimated that the results of NIH-supported research were published in approximately 60,000 to 65,000 articles based on the number of articles published in the last several years that contained an NIH grant number within the text. We will estimate participation by comparing the actual number of papers deposited in the NIH Manuscript Submission (NIHMS) system for a given interval with the historical average. For example, 5,000 deposited articles per month would indicate approximately 100 percent participation. By the close of the calendar year sufficient data should be available to make an assessment of the degree of participation. Statistics for the distribution of the embargo periods requested by authors will be readily available from the submission system.

QUESTIONS SUBMITTED BY SENATOR DANIEL K. INOUYE

CANCER COUNCIL OF THE PACIFIC ISLANDS

Question. The Cancer Center in Hawaii continues to provide vital research that will benefit Native Hawaiians, Pacific Islanders, and the world community. Last year, the Senate requested that a task force review the continuing and unique needs of Native Hawaiians and Pacific Islanders, specifically as those findings relate to the higher incidence of some types of cancers in these populations. Please provide an update from the Director's task force on your findings.

Answer. As recommended by the work of National Cancer Institute's (NCI) task force in the Pacific Rim, NCI has created the Cancer Council of the Pacific Islands (CCPI), a community-and region-based council comprised of representatives of the professional native physicians and other health professionals representing the six

U.S.-associated jurisdictions of the Pacific to address the cancer health needs within each of these jurisdictions. NCI has supported the development of this task force and conducted needs assessments in all jurisdictions, and continues to support capacity building and to address high priority cancer needs in these communities. The CCPI provides a community-based forum through which all federal agencies conducting programs in these jurisdictions coordinate efforts.

The accomplishments of the Cancer Council of the Pacific Islands are substantial. These accomplishments are also significant in that, for the first time, Island leaders are provided a controlling voice in the design, development, and implementation of their own survey instrument and subsequent activities. With the assistance of selected professors and students from the University of Hawaii, a comprehensive cancer assessment was administered in Kosarae, Chuuk, Pohnpei, Yap, Belau, Marshall Islands (Ebeye, Majuro), Northern Mariannas, American Samoa, and Guam. We are now implementing the prioritized listings of health needs identified as a result of those assessments.

NCI recently awarded a 5-year Community Networks Cooperative Agreement to the Lyndon Baines Johnson Tropical Medical Center in American Samoa to directly address cancer disparities, train minority investigators, reduce access barriers, and provide research infrastructure to link American Samoa to NCI research—Cancer Information Service (NCI's cancer information helpline), innovated screening, and diagnostic technologies and clinical trials, in particular.

Recently, the CCPI met with NCI, the Health Resources and Services Administration, the Centers for Disease Control and Prevention (CDC), and other federal partners, as well as C-Change (a coalition of the nation's key cancer researchers and policymakers), to work on developing Comprehensive Cancer Plans for each jurisdiction, and a regional plan for the Pacific Rim. NCI is providing technical assistance and administrative support to augment CDC's efforts in developing these plans. Once these plans are developed, each jurisdiction and the CCPI will be able to apply for CDC implementation funds. NCI is committed to this community-based effort in the Pacific Rim and continues to develop collaborative programs for the CCPI with federal agencies who can improve the health and well-being of the Pacific Island communities.

CANCER AND ETHNICITY

Question. Additionally, I chaired hearings in Honolulu during which data was presented showing striking differences in the incidents of cancer among various ethnic groups. I am told the FDA now encourages clinical testing for new drugs in a variety of ethnic groups because the drugs themselves have a different effect on each group. Has NIH or NCI been pursuing additional research on the genetic or cultural causes of cancer and the efficacy of treatment by different ethnic groups?

Answer. Two years ago, the National Cancer Institute (NCI) launched the Breast and Prostate Cancer and Hormone-related Gene Variants Cohort Consortium (BPC3 Study) to pool data and biospecimens from 6 large cohorts to conduct research on gene-environment interactions in cancer etiology. One of these cohorts, the Multiethnic Cohort (MEC) Study, is evaluating the genetic and biochemical determinants of cancer risk in traditionally understudied minority populations and consists of 215,251 men and women (ages 45–75 years at baseline) from Hawaii (Asians, Whites, and Native Hawaiians) and California (African-Americans and Latinos). NCI has begun a Minority Accrual Initiative, whose goals include increasing the number of minority investigators and minority patients in cancer research. The University of Hawaii received funding to foster minority accrual to clinical trials through this initiative. Historically, the University of Hawaii and its affiliated hospitals have accrued large numbers of minority patients, both Asian-Americans and Native Hawaiians, to prevention and treatment trials.

NCI has also encouraged collaborations between sites with relatively non-diverse populations (e.g., Rochester, Minnesota) and sites with large minority populations (e.g., Wayne State, Howard University) to increase minority accrual to early clinical trials where substantial data regarding variations in drug disposition can be acquired. Drug disposition data from all NCI's Cancer Therapy Evaluation Program trials is evaluated to determine whether any differences are evident for these subcategories of patients. In addition, Phase 3 clinical trials are analyzed for differences in outcome according to race and age among other factors and have resulted in publications in these areas and new research approaches to eliminate disparities. The bioinformatics infrastructure that supports these clinical trials will facilitate even greater data sharing across trials and more robust comparisons and data analysis in the future.

In a public-private partnership, NCI has funded seven sites to explore approaches to improve accrual of minority and older patients to early clinical trials. In addition, for large clinical trials groups that accrue approximately 25,000 patients per year to NCI sponsored clinical trials, there are a number of specially funded programs that focus on increasing the accrual and evaluation of under-represented racial, ethnic, and demographic groups (elderly and rural) to clinical trials. These include supplements to specific programs in the NCI Clinical Cooperative Groups and the long-standing Minority-Based Cancer and Community Oncology Program. There is also a large program funded in collaboration with the National Institute of General Medical Sciences that supports a Pharmacogenetics Network. This Network evaluates pharmacogenomics in drug development which includes the study of the impact of race/ethnicity on drug efficacy.

Question. How satisfied are you with the amount and quality of research done in this area?

Answer. Preliminary findings from the Hawaii Tumor Registry show that foreign-born Asians, when compared to U.S.-born Asians and Caucasians, have a lower percentage of cancer diagnosed at an early stage, a higher percentage of cancer diagnosed at a late stage, and lower rates of cancer survival. In an effort to overcome these disparities, we have strengthened NCI community-based programs in Hawaii including the Community Network Program, Imi Hale Native Hawaiian Cancer Network, the American Samoa Community Cancer Network at the Lyndon B. Johnson Tropical Medical Center in American Samoa, and strengthening support for the Cancer Research Center of Hawaii, a NCI-designated cancer research center whose mission is to bring together researchers who focus on understanding the etiology of cancer and on reducing its impact on the people of Hawaii.

NCI expects to continue to expand research in cancer health disparities to increase our understanding of why some populations experience greater incidence, mortality, and lower survival from cancer than the majority of Americans. In the NCI report, Making Cancer Health Disparities History, published in March 2004, a Trans-HHS Cancer Health Disparities Progress Review Group (PRG) comprised of leading cancer experts, researchers, patients, cancer survivors, and advocates in cancer and health disparities reviewed the status of cancer health disparities in the United States and forged a set of 14 priority recommendations for Department of Health and Human Services (HHS) to lead the Nation in eliminating cancer health disparities. On March 28, 2005, the HHS Health Disparities Council established a Subcommittee on Cancer with NCI as its chair. The subcommittee will focus on six of the PRG's 14 recommendations that will address needs ranging from the planning and coordination of program efforts to discovery, development, and delivery of research advances to all Americans.

Communities, caregivers, and researchers must form strong alliances and explore creative solutions for developing culturally competent venues for service delivery. Community-based participation must be an integral part of the planning, development, and implementation of solutions to bring research advances to all populations. This cross fertilization will build synergism and ensure stronger, more dynamic alliances for overcoming cancer health disparities.

BEHAVIORAL RESEARCH

Question. Since 1999, the Committee's report has urged the National Institute of General Medical Sciences (NIGMS) to fund basic behavioral research. The legislative mandate for NIGMS specifically includes behavioral science research, yet I am not satisfied basic behavioral research has been adequately or even minimally addressed. I understand a working group was established as part of the NIH Advisory Committee to the Director on Research Opportunities in the Basic Behavioral and Social Sciences. I feel we have been extremely patient and sufficient time has elapsed to review this issue. Please provide a report to the Committee outlining the recommendations of the working group and your timeline for implementation.

Answer. In keeping with the preferred approach of performing portfolio analysis across NIH rather than on an institute-by-institute basis, a working group of the Advisory Committee to the Director, NIH, was formed to examine basic behavioral research across NIH. The working group reported to the Advisory Committee on December 2, 2004. Their analysis revealed that the institutes and centers (including NIGMS) supported approximately $2.68 billion in behavioral research, including approximately $936 million in basic behavioral research, in fiscal year 2003. In addition to this base, several components of the NIH Roadmap for Medical Research are directed toward basic behavioral research. In particular, several mechanisms are being used to stimulate interdisciplinary research at the interface of the behavioral/social and biological sciences, provide the interdisciplinary training necessary for

postdoctoral investigators to work in these areas, and support development of innovative methods and technology that will facilitate research at the intersection of the behavioral, social and biomedical sciences.

Following the submission of the working group report, NIGMS has taken several steps to more clearly articulate the basic behavioral research it supports, encourage the submission of more research applications in these areas, and increase the number of investigators who can work at the interface of the behavioral and biological sciences:

Research Training at the Interface of the Behavioral and Biological Sciences.—Basic behavioral research is of critical importance to the mission of the NIH and can play a crucial role in understanding the etiology of disease and enhancing preventive and therapeutic inventions. Greater understanding of the molecular, genetic, and neural processes governing behavior, and the reciprocal effects of behaviors on physiological processes, is crucial for a complete understanding of human health and those diseases in which behavior is a risk factor, diagnostic indicator, or symptom. To advance our knowledge in these areas, researchers will need to integrate multiple disciplinary perspectives, methodologies, and levels of analysis. NIGMS has a strong background in developing and supporting such interdisciplinary research training. While some existing NIGMS training programs such as the Medical Scientist Training Program and the Systems and Integrative Biology program include elements of the behavioral sciences, there has not been a program dedicated to training at the basic behavioral science-biological science interface. NIGMS has developed a proposal for such a predoctoral. program and is coordinating its further development with other NIH Institutes having an interest in this area.

Collaborative Research on Basic Mechanisms of Behavior.—To encourage the multidisciplinary research that is needed for a fuller understanding of the basic mechanisms of behavior, NIGMS has proposed an initiative to facilitate collaborations between basic behavioral scientists and investigators with expertise in state-of-the-art genetics, molecular biology, and genomics. It is anticipated that this collaborative research, performed with model organisms, will either enhance existing models or lead to the development of new models of normal or abnormal human behavior. The concept for this solicitation is to be presented for approval at the May 2005 meeting of the National Advisory General Medical Sciences Council.

Assessing Interactions Among Social, Behavioral, and Genetic Factors in Health.—NIGMS is a major contributor to an Institute of Medicine committee examining the state of the science on gene-environment interactions that affect human health. The study will identify approaches and strategies to strengthen the integration of social, behavioral, and genetic research in this field as well as consider relevant training and infrastructure needs. The results of this study will be used by the NIH to guide its programs in these areas.

QUESTIONS SUBMITTED BY SENATOR HARRY REID

CHRONIC FATIGUE SYNDROME

Question. Funding for research on chronic fatigue syndrome (CFS) has fallen to less than $5 million per year, at the same time national prevalence estimates for this serious condition have risen to nearly one million American adults and adolescents. In June 2003, Dr. Vivian Pinn announced plans to issue a Request for Applications (RFA) for research on CFS following an NIH workshop on neuro-immune mechanisms in CFS. Almost two years later this RFA has not been issued. What are NIH's immediate plans to stimulate research into CFS, a condition that CDC reports costs the U.S. economy $9.1 billion a year in lost productivity?

Answer. Funding levels for CFS have remained at approximately $5–$6 million a year without a significant decline in dollars in years. NIH continues to encourage an increase in the number of CFS research proposals that are submitted for review and funding each year. Applications to PA–02–034, The Pathophysiology and Treatment of Chronic Fatigue Syndrome, based on recommendations from an October 2000 symposium, tripled from its release in December 2001 through fiscal year 2004. This PA was revised and reissued under the same title as PA–05–030 in December 2004 to include research ideas from the June 2003 scientific workshop, Neuroimmune Mechanisms and Chronic Fatigue Syndrome: Will Understanding Central Mechanisms Enhance the Search for the Causes, Consequences, and Treatment of CFS? This program announcement specifically invites the submission of investigator-initiated grant applications to support research on the epidemiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the life span. Applications that address gaps in the understanding of the environmental and

biological risk factors, the determinants of heterogeneity among patient populations, and the common mediators influencing multiple body systems that are affected in CFS are encouraged.

The proceedings of this June 2003 workshop were recently published (NIH Publication No. 04–5497) and posted on the ORWH/CFS website (http://www4.od.nih.gov/orwh/cfs-newhome.html). Seven new projects related to CFS were funded in fiscal year 2004 and address topics raised at this workshop. One of these is an intramural project which reflects the impact of a new Trans- NIH Intramural Interest Group on Scientific Integrative Medicine that resulted from the June 2003 CFS Workshop. Also based on this workshop, the ORWH and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome will be issuing a new interdisciplinary Request for Applications (RFA) later in fiscal year 2005. This new RFA on CFS has progressed through the usual steps following the workshop when the intent was announced. In addition, NIH continues to plan relevant scientific activities and efforts on which to base future CFS research initiatives.

Question. Last fall, an analysis of NIH funding for chronic fatigue syndrome (CFS) was presented to the DHHS CFS Advisory Committee by the CFIDS Association of America. This report documented that NIH had overstated its funding of CFS research for fiscal year 1999-fiscal year 2003 by 19.6 percent through the inclusion of studies unrelated to CFS. Total funding of CFS research for this five-year period is just $26 million—a very small amount given magnitude of the condition and the generous increases Congress provided to NIH during these same years. What efforts are being taken to ensure that spending figures issued by NIH are accurate and reliable and what is NIH doing to expand support of research on CFS?

Answer. The funding figures provided by the NIH on expenditures related to CFS are based upon the best scientific and budgetary deliberations and are consistent and accurate. As with all scientific and budgetary data collections, these funding figures reflect projects designated as CFS research by Institute and Center (IC) staff, each utilizing his/her best scientific judgment. These figures include funding for basic and laboratory studies that are pivotal in the development of clinical and translational research; although such studies may not seem specific for CFS, they deal with the basic biologic processes that are fundamental to developing a better understanding of CFS and are thus integral to CFS research. The NIH continues to implement efforts to increase CFS research through an increase in funded proposals.

QUESTIONS SUBMITTED BY SENATOR HERB KOHL

EPILEPSY RESEARCH

Question. As you know, epilepsy is a major public health problem, affecting 2.5 million Americans throughout their life spans. The impact of epilepsy—ranging from debilitating side-effects of treatment to brain damage and even death—has long been under-recognized. Epilepsy is a public health problem of major proportions.

Because epilepsy may occur at any age and as a result of many different, poorly understood and complicated causes, Congress has encouraged the NIH to focus on this problem with a multi-disciplinary approach involving efforts by the NIMH, NIA, NICHD and NHGRI in coordination with the lead institute, NINDS.

Epilepsy is the perfect model for a disease that will succumb to a coordinated, multi-disciplinary research effort such as you outlined in "The NIH Neuroscience Blueprint". A few of the above-mentioned Institutes have begun to address epilepsy, but coordination and communication between them is a necessity if this multi-disciplinary approach is to prove fruitful.

It seems critically important to establish a working group to coordinate research efforts, clinical trials and learn from the co-morbidities which are so common in patients with epilepsy. Dr. Zerhouni, how do you intend to facilitate the coordination which needs to exist between these research efforts in order to reduce the burden of this all-too-common neurological disorder?

Answer. The National Institute of Neurological Disorders and Stroke (NINDS) is the lead NIH Institute for epilepsy research and the primary funding source for studies of seizure disorders. Several other NIH Institutes and Centers also fund epilepsy related projects, including the National Institute of Child Health and Human Development (NICHD), the National Human Genome Research Institute (NHGRI), the National Institute of Mental Health (NIMH), and the National Institute on Aging (NIA). In order to better facilitate coordination of research efforts in this area, these Institutes formed an Interagency Epilepsy Working Group. Since its establishment in January 2003, several other NIH Institutes with an interest in epilepsy re-

search have joined, including the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the NIH John E. Fogarty International Center (FIC), as well as a representative from the National Center for Chronic Disease Prevention and Health Promotion at the Centers for Disease Control and Prevention (CDC).

The members of the Interagency Epilepsy Working Group are primarily extramural program staff who administer epilepsy research grants and develop program activities to facilitate research efforts. The purpose of this group is to increase communication among institutes and agencies supporting epilepsy related research and to explore opportunities for increased coordination. An example of these cooperative activities is a recent workshop sponsored by the NINDS and the NIMH on the treatment of non-epileptic seizures, held on May 1–3, 2005. The goals of the workshop were to better define diagnostic criteria for non-epileptic seizures, develop outcome measures for clinical trials, and to discuss a research strategy for this condition.

The Interagency Epilepsy Working Group meets on a regular basis, most recently in October 2004 and April 2005. The April Working Group meeting focused on the development of biomarkers for epilepsy related research. Working Group members presented examples of relevant Institute activities which could be adapted to epilepsy and discussed possible approaches to planning a workshop in this important area of research. In addition, members of the Working Group participated in the most recent meeting of the Epilepsy Benchmark Stewards in February 2005. The Epilepsy Benchmarks are milestones developed by the epilepsy community in 2001 to measure progress in epilepsy research, and Stewards have been designated to monitor progress toward meeting each Benchmark goal. The purpose of the February meeting was to review Benchmark progress and to begin planning a large epilepsy conference for 2007 to assess and update the Epilepsy Benchmarks. Working Group members will continue to be involved as conference planning progresses.

K30 GRANT AWARDS

Question. As you know, the K30 grant program supports the training of clinical researchers—health professionals who translate laboratory discoveries to improvements in the care of patients. It is my understanding that this year, funding was insufficient to accommodate a decision to increase the size of awards from $200,000 to $300,000, resulting in the University of Wisconsin losing their K30 award as of June. While I applaud your efforts to increase the award amount, I am concerned that programs like the one at Madison, who depend on K30 grants, will be forced to close their doors.

The shortage of clinical researchers trained to advance medical science and improve the care of patients has been well-documented in reports from the National Academy of Sciences and the NIH. The University of Wisconsin's program has trained 144 clinical researchers to date. What will you do to ensure the K30 grant program is funded at a level sufficient to restore and expand the program at the $300,000 level?

Answer. The NIH recognizes the need for clinical research training to ensure that the nation's needs for clinician researchers are met. As such we have a number of programs designed to create well-trained patient-oriented researchers. A major part of this effort is the Clinical Research Curriculum Award (K30). To help address the needs of this specific trans-NIH program, a decision was made to increase the total funds available from $10,958,000 in fiscal year 2004 to $14,700,000 in fiscal year 2005. Additionally, all Institutes and Centers funding clinical research will contribute to these awards and the size has been increased to $300,000. While we realize that we cannot fund all meritorious applications, we do expect to award 49 grants out of the 81 applications received which is a 61 percent success rate.

IRRITABLE BOWEL SYNDROME

Question. Dr. Zerhouni, for the last several years, my colleagues and I on the Appropriations Committee have asked NIDDK to develop a strategic plan for research into Irritable Bowel Syndrome (IBS), a chronic complex of disorders that malign the digestive system. Can you update this Committee on the timetable for development and implementation of a strategic plan for IBS at NIDDK?

Answer. The NIH concurs that a strategic plan for IBS will identify areas of scientific opportunity and serve as a stimulus in the prevention, diagnosis, and management of this functional disorder. Due to recent Congressional interest, the NIH is in the early stages of creating a new Commission on digestive diseases, which will develop a long-range research plan for the entire spectrum of these diseases, including IBS.

The congressional directive to establish the Commission is in the Senate report language accompanying the Labor/HHS appropriations bill (Senate Report 108–345, page 165). In documentation accompanying the President's Budget request for fiscal year 2006, the NIH has informed the Labor/HHS appropriations committees that it considers the establishment of the commission at this time to be both appropriate and useful (HHS fiscal year 2006 Justification of Estimates for Appropriations Committees, pp. OD 64–65).

This Commission will perform an assessment of the state-of-the-science in digestive diseases and develop a Long-Range Research Plan for Digestive Diseases—with broad stakeholder input from scientific and lay experts. A parallel effort, under the leadership of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), will compile current data on the burden of digestive diseases, which would also feed into the Commission's planning process. As noted in the draft charter for the Commission, the Long-Range Research Plan would focus solely on research—consistent with the NIH mission.

The Commission is important because the Long-Range Research Plan it develops will serve as a beneficial scientific guidepost to both the NIH and the digestive diseases community, and would serve the public health. According to recent estimates, the total costs associated with major forms of digestive diseases approach $43 billion annually. The Plan will focus on research in specific diseases, including IBS, and will also address the training and education of researchers in digestive diseases research; programs for the collection, dissemination, and exchange of information and resources in health and disease relevant to digestive diseases research; and identification of cross cutting, innovative research disciplines and technologies and opportunities for synergy in both basic and clinical research within the Institutes and Centers of the NIH. The inclusion of IBS as a part of a larger strategic planning effort, instead of conducting a stand-alone IBS planning effort, will provide greater opportunity to identify cross-cutting themes common to multiple digestive diseases and common hurdles shared by many.

AGE-RELATED MACULAR DEGENERATION

Question. I understand that the rate of occurrence of age-related macular degeneration (AMD) will double over the next 15 years, robbing our seniors of their sight. Can you tell us about the research into this disease, and specifically, what therapies may be emerging to stop or reverse this trend?

Answer. The National Institutes of Health strongly supports research for age-related macular degeneration (AMD) and has contributed greatly to the understanding of the disease and to the development of new therapies for the disease. Four recently published studies supported by the National Eye Institute report on the identification of inherited variations in a gene that greatly increase the risk of developing AMD. The gene, known as complement factor H, is involved in the body's immune defense system. These findings suggest a possible role for inflammation in the cascade of biological events that leads to AMD. This important discovery may lead to development of new approaches to preventing, diagnosing, and treating this disease.

The National Eye Institute conducted Age-Related Eye Disease Study (AREDS) found that a daily high-dose specific formulation of antioxidants and zinc can slow the progression of AMD from intermediate to advances stages of the disease. Based on an analysis of prevalence data and the AREDS study findings, it is estimated that more than 300,000 Americans could avoid developing advanced AMD and its associated vision loss over the next five years by taking this formulation.

An advanced form of AMD called "wet" AMD develops as a result of new, abnormal blood vessels that grow beneath the retina, leak blood and fluid, and produce scar tissue. Left untreated, catastrophic loss of central vision may occur. The FDA has approved two new treatments, verteporfin and pegaptanib, for controlling "wet" AMD. These newly approved treatments were developed by industry, but benefited from early support for basic research that provided a better understanding of the underlying biology. A number of even newer treatments, also aimed at preventing or reducing this abnormal blood vessel growth in AMD, are being evaluated in ongoing clinical trials.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

DRUG RESEARCH AND DEVELOPMENT

Question. NIH has made tremendous contributions to the public good through investments in medical research and therapeutic clinical trials. I'm troubled, though,

that U.S. citizens are paying twice for pharmaceuticals, once through taxpayer support for NIH-funded research and then again at the pharmacy when they purchase the drugs that NIH funding helped to develop.

For example, I have a hard time believing that prices charged for drugs like Taxol, AZT, Gleevec, and others that are substantially funded by taxpayer money are fair.

Is there anything NIH can do to retain or recoup some of the market value of these therapies that are developed based on NIH-funded research?

Answer. Since 2003, NIH has executed 610 new licenses and has collected $112 million in royalty income from its intramural research program. This represents about two-thirds of the royalty income collected by all federal agencies. Most of NIH's licenses are executed for early-stage technologies with small companies that do not yet have product sales. NIH, however, carefully crafts its licensing terms so that it captures a reasonable share of the profits for those products that achieve commercialization. In addition, NIH has established a Monitoring and Enforcement Branch in the Office of Technology Transfer dedicated to monitoring the expeditious development of our licensed technologies and to ensuring that we receive the full return on our investment.

In May 2000, the U.S. Congressional Joint Economic Committee issued The Benefits of Medical Research and the Role of NIH, which examined the role of federal funding for medical research and the benefits that derive from that research. The Committee report concluded that the benefit of increased life expectancy to the United States as a result of advances in health care from NIH-funded medical research results in a payoff of about 15 times the taxpayers' investment in NIH. Clearly, there are financial and public health related benefits of remarkable value that flow from NIH-funded biomedical research.

The NIH contributes to affordability by conducting and funding research that leads to the development of a wider selection of drugs or new drugs, where no drugs were available. More alternatives can translate into more choices for the public, greater market competition, affordability and, ultimately, overall return to society by the improvement of the quality of life. Thus, as long as NIH continues to focus on its core mandate, namely conducting and funding broad-based research that could lead to the development of new drugs and therapies in the future, we believe that NIH is acting as a responsible partner in the national enterprise to improve the quality of life for the public and to make drugs more affordable.

PUBLIC ACCESS

Question. Your first steps toward more readily accessible research information for the public are commendable and appropriate. As I understand the process, the results of NIH-funded research should be available 12 months after it is published.

But why are you proposing that making research results accessible to the public is "recommended?" If this is such a good idea—and I think it is—why isn't it required?

Answer. The voluntary nature of the Policy was established to encourage investigators to deposit their manuscripts in NIH's public archive. We believe this approach will ultimately result in broader participation. The Policy-related submissions will directly benefit NIH-supported investigators because recent studies have shown that freely available articles get cited more in other research publications. An increase in the number of citations helps improve the professional standing of investigators. Due to these benefits we anticipate that authors will decide to participate and to choose the earliest release dates.

I also believe that the voluntary nature of the final policy permits sufficient flexibility to accommodate the needs of different stakeholders and leaves the ultimate decision in the hands of scientific investigators who are in the best position to judge the circumstances and the time frame under which their work may be made accessible to the public at large. Therefore, we believe that by having a Policy that provides maximum flexibility, authors will respond with maximum participation.

Question. A year's delay after publication in a journal strikes me as a very long time, given the pace of biomedical developments today. How much time do you expect most participating researchers to let go by between publication and release of the study publicly?

Answer. The Public Access Policy strongly encourages all NIH-funded researchers to make their peer-reviewed author's final manuscripts available to other researchers and to the public at the National Library of Medicine's (NLM) PubMed Central (PMC) immediately after the official date of final publication. At the time of submission, authors are also given the option to release their manuscripts at a later time,

up to 12 months after publication. NIH expects that only in limited cases will authors deem it necessary to select the longest delay period.

The Policy-related submissions will directly benefit NIH-supported investigators by offering an alternate means by which they can fulfill the existing requirement to provide publications as part of progress reports. It is anticipated that, in the future, investigators applying for new and competing renewal support from the NIH will also utilize this resource by providing links in their applications to their PubMed Central-archived information. Further, recent studies have shown that freely available articles get cited more in other research publications. Increased citations help improve the professional standing of investigators. Due to these benefits we anticipate authors will choose the earliest release dates.

Question. What rates of participation and time delays would you consider a success?

Answer. Our goal is to build a comprehensive archive of the results of research that NIH funds. Rather than specifying a particular target number, we will be looking for an increasing number of manuscripts to be submitted over time and a decreasing delay period. Issuance of this policy is the beginning of a process that will include refinements as experience develops, outcomes are evaluated, and public dialogue among all the stakeholders is continued. An NIH Public Access Working Group of the NLM Board of Regents has been established. The Working Group includes representatives of the various stakeholder groups and will advise the NLM Board of Regents on implementation and assess progress in meeting the goals of the NIH Public Access Policy. Once the system is operational, modifications and enhancements will be made as needed based on the recommendations of the Working Group, or a permanent subcommittee of the Board, providing ongoing advice on improvements.

We hope that secondary effects of the Policy might also be viewed in terms of "success." Since the Proposed Policy's release in September 2004, we have heard that an increasing number of publishers, within and outside of the United States, are considering changes to or adoption of Open Access publishing models. For example, in January the Nature Publishing Group altered its open access model to increase accessibility to its publications. We are optimistic that these changes will provide the public with free electronic access to Journal articles, through the publisher's web site, on a faster time scale or for the first time. This "change in the landscape" complements the benefits of the NIH Policy since the majority of articles in Journals (approximately 90 percent) do not result from NIH-funded research.

SUBCOMMITTEE RECESS

Senator HARKIN. Thank you very much.

The subcommittee will stand in recess to reconvene at 9:30 a.m., on Monday, July 11 in room SD–192. At that time we will hear testimony from the Honorable Patricia Harrison, President and CEO, Corporation for Public Broadcasting.

[Whereupon, at 11:18 a.m., Wednesday, April 6, the subcommittee was recessed, to reconvene at 9:30 a.m., Monday, July 11.]